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(54) Title: GLUCAGON ANTAGONISTS/INVERSE AGONISTS

(57) Abstract

Non–peptide compounds comprising a central hydrazide motif and methods for the synthesis thereof. The compounds act to antagonize the action of the glucagon peptide hormone.

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GLUCAGON ANTAGONISTS/INVERSE AGONISTS

Field of the invention

The present invention relates to agents that act to antagonize the action of the glucagon peptide hormone. It relates particularly to non-peptide glucagon antagonists or inverse agonists.

Background of the invention

Glucagon is a key hormonal agent that, in co-operation with insulin, mediates homeostatic regulation of the amount of glucose in the blood. Glucagon primarily acts by stimulating certain cells (mostly liver cells) to release glucose when blood glucose levels fall. The action of glucagon is opposed by insulin which stimulates cells to take up and store glucose whenever blood glucose levels rise. Both glucagon and insulin are peptide hormones.

Glucagon is produced in the alpha islet cells and insulin in the beta islet cells of the pancreas. Diabetes mellitus, the common disorder of glucose metabolism, is characterized by hyperglycemia, and can present as type I, insulin-dependent, or type II, a form that is non-insulin-dependent in character. Subjects with type I diabetes are hyperglycemic and hypoinsulinemic, and the conventional treatment for this form of the disease is to provide insulin. However, in some patients with type I or II diabetes, absolute or relative elevated glucagon levels have been shown to contribute to the hyperglycemic state. Both in healthy animals as well as in animal models of type I and II, removal of circulating glucagon with selective and specific antibodies has resulted in reduction of the glycemic level (Brand et al. Diabetologia 37, 985 (1994); Diabetes 43, [suppl 1], 172A (1994); Am J Physiol 269, E469-E477 (1995); Diabetes 44 [suppl 1], 134A (1995); Diabetes 45, 1076 (1996)). These studies suggest that glucagon suppression or an action antagonistic to glucagon could be a useful adjunct to conventional antihyperglycemia treatment of diabetes. The action of glucagon can be suppressed by providing an antagonist or an inverse agonist, substances that inhibit or prevent glucagon induced response. The antagonist can be peptide or non-peptide in nature. Native glucagon is a 29 amino acid-containing peptide having the sequence:

His-Ser-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-NH_2.

Glucagon exerts its action by binding to and activating its receptor, which is part of the Glucagon-Secretin branch of the 7-transmembrane G-protein coupled receptor family (Jelinek et al. Science 259, 1614, (1993)). The receptor functions by activation of the adenylyl cyclase second messenger system and the result is an increase in cAMP levels.

Several publications disclose peptide antagonists. Probably, the most thoroughly characterized antagonist is DesHis^1[Glu^9]-glucagon amide (Unson et al., Peptides 10, 1171 (1989); Post et al., Proc. Natl. Acad. Sci. USA 90, 1662 (1993)). Other antagonists are eg DesHis^1,Phe^6[Glu^9]-glucagon amide (Azizh et al., Bioorganic & Medicinal Chem. Lett. 16, 1849 (1995)) or NLeu^9,Ala^{11,16}-glucagon amide (Unson et al., J. Biol. Chem. 269(17), 12548 (1994)).

Peptide antagonists of peptide hormones are often quite potent; however, they are defective as drugs because of degradation by physiological enzymes, and poor biodistribution. Therefore, non-peptide antagonists of the peptide hormones are preferred. Among the non-peptide glucagon antagonists, a quinoxaline derivative, (2-styryl-3-[3-(dimethylamino)propylmethylamino]-6,7-dichloroquinoxaline was found to displace glucagon from the rat liver receptor (Collins, J.L. et al. (1992) Bioorganic and Medicinal Chemistry Letters 2(9):915-918). West, R.R. et al. (1994), WO 94/14426 discloses use of skyrin, a natural product comprising a pair of linked 9,10-anthracenedione groups, and its synthetic analogues, as glucagon antagonists. Anderson, P.L., U.S. Patent No. 4,359,474 discloses the glucagon antagonistic properties of 1-phenyl pyrazole derivatives. Barcza, S., U.S. Patent No. 4,374,130, discloses substituted disilacyclohexanes as glucagon antagonists. WO 98/04528 (Bayer Corporation) discloses substituted pyridines and biphenyls as glucagon antagonists. Furthermore, WO 97/16442 (Merck & Co., Inc.) discloses substituted pyridyl pyrroles as glucagon antagonists and WO 98/21957 (Merck & Co., Inc.) discloses 2,4-diaryl-5-pyridylimidazoles as glucagon antagonists. These glucagon antagonists differ structurally from the present compounds.

Description of the invention

Definitions

The following is a detailed definition of the terms used to describe the compounds of the invention:

The term "C_{1-6}-alkyl" as used herein, alone or in combination, represents a branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Typical C_{1-6}-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, hexyl, isohexyl and the like.

The term "C_{1-6}-alkoxy" as used herein, alone or in combination, refers to the group -O-C_{1-6}-alkyl where C_{1-6}-alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

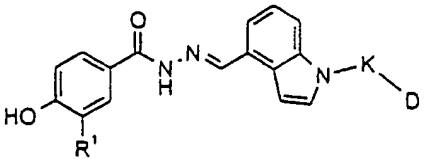
The term "C_{3-8}-cycloalkyl" as used herein, alone or in combination, represents a carbocyclic group having from 3 to 8 carbon atoms eg cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The term "halogen" as used herein means Cl, Br, I, or F.

Description of the invention

The present invention is based on the unexpected observation that compounds having a selected nitrogen-bearing central motif and the general structural features disclosed below antagonize the action of glucagon.

Accordingly, in one aspect the invention relates to 1,4-substituted indoles of the formula (I):



(I)

wherein

R^1 is chloro, fluoro, nitro or cyano;

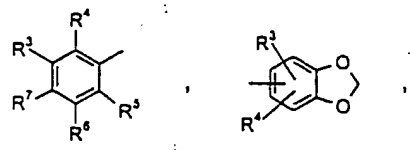
K is $-C(O)-(CH_2)_d-$, $-CH_2-CH_2-O-$ or $-CHR^2-$;

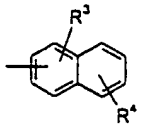
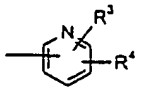
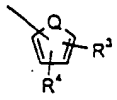
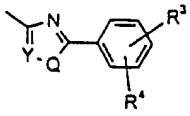
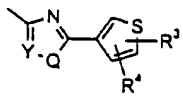
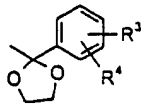
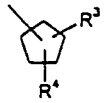
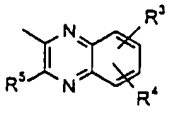
wherein

d is 0 or 1;

R^2 is hydrogen or C_{1-6}-alkyl ;

D is

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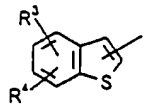


wherein

Q is -O- or -S-;

Y is -CH= or -N=;

R^3, R^4, R^5, R^6 and R^7 independently are hydrogen, C_{1-6}-alkyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, halogen, carboxamido, hydroxymethyl, phenyl, dimethylamino, C_{1-6}-alkoxy or nitro;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

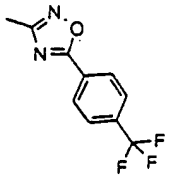
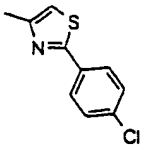
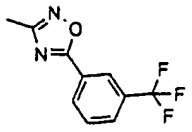
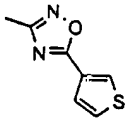
In a preferred embodiment R^1 is chloro.

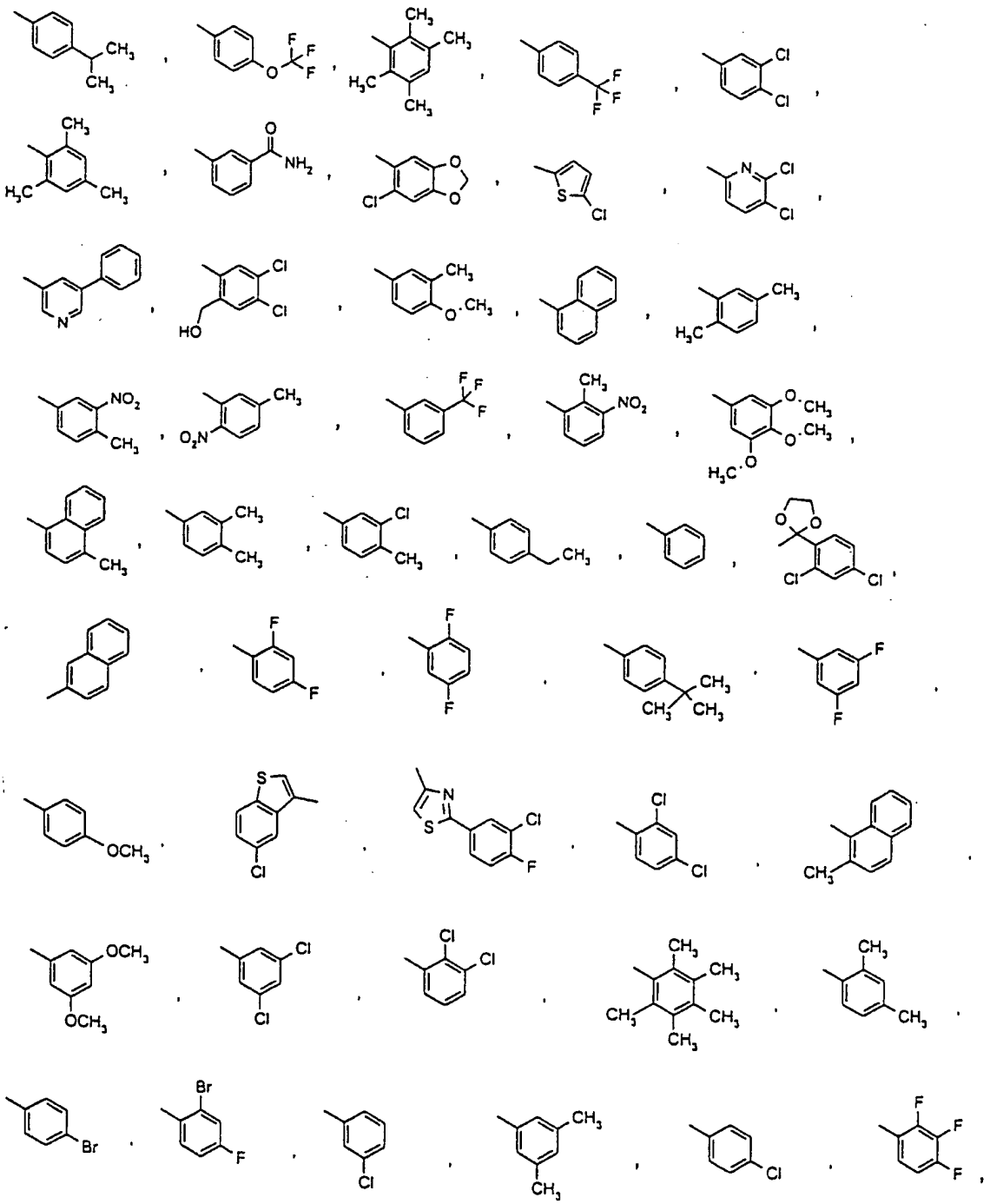
More preferred R^1 is cyano.

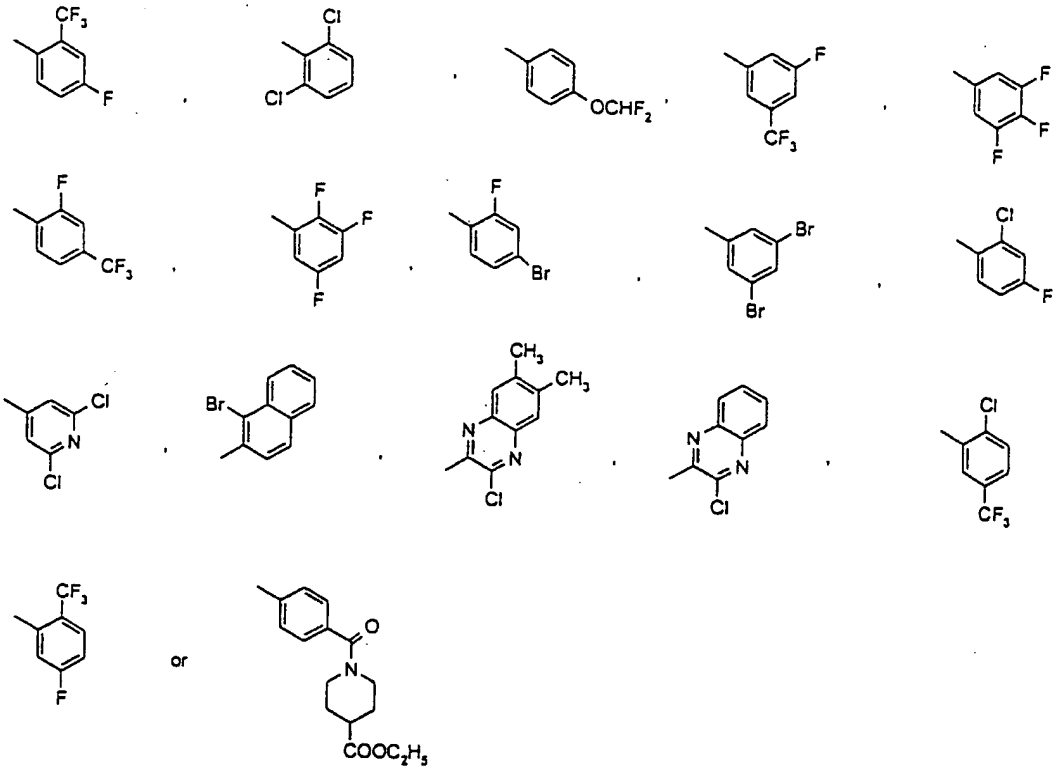
In a further preferred embodiment K is $-CH_2-$ or $-CH(C_{1-6}\text{-alkyl})-$.

In another preferred embodiment K is -C(O)- or $-C(O)-CH_2-$.

In yet another preferred embodiment D is





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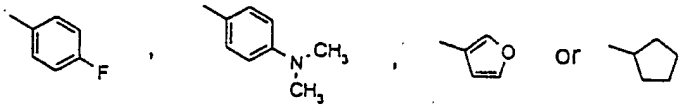
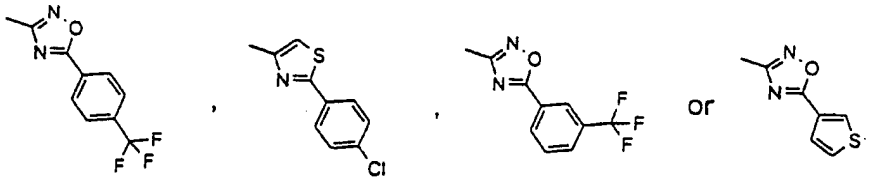
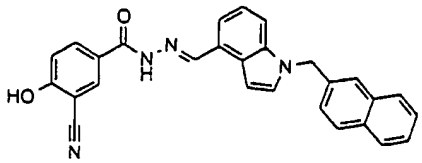
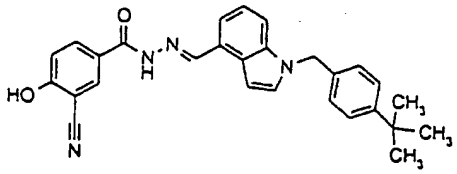


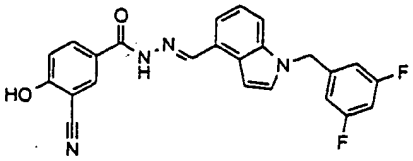
In still a further preferred embodiment D is

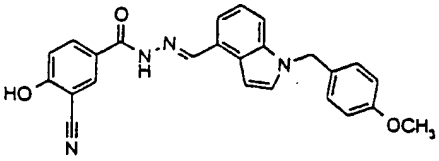


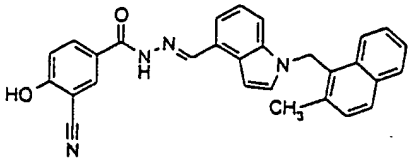
In another preferred embodiment the invention relates to the following compounds of the formula (I):

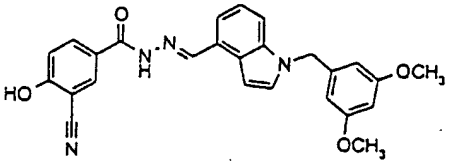


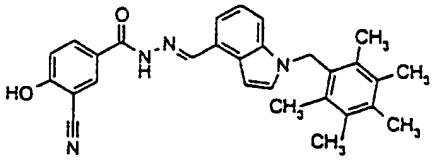


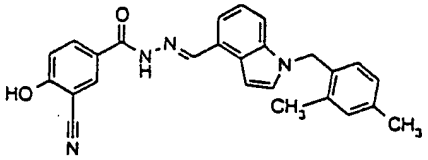


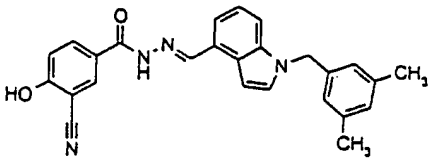


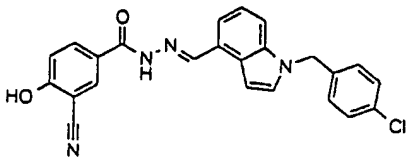


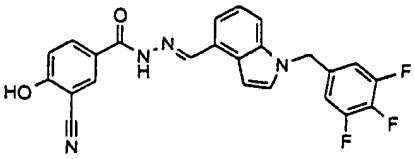


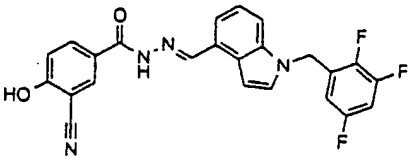


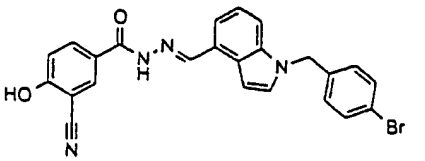


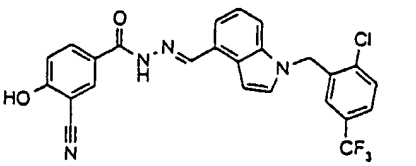


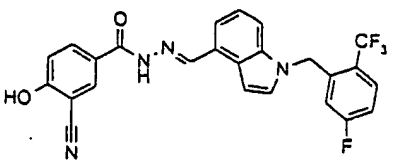


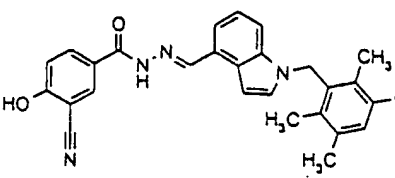


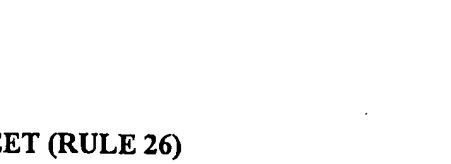












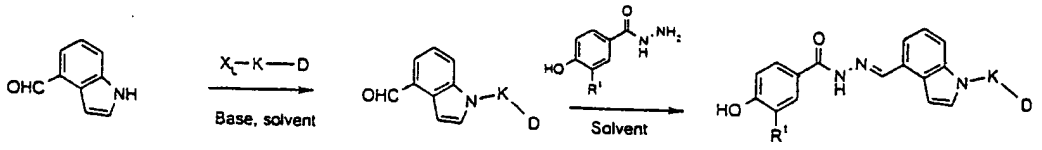
as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

The present invention is further illustrated by the following representative examples which are, however, not intended to limit the scope of the invention in any way. The following synthesis protocols refer to intermediate compounds and final products identified in the specification and in the synthetic schemes. The preparation of the compounds of the present invention is described in detail using the following examples, but the chemical reactions described are disclosed in terms of their general applicability to the preparation of the glucagon antagonists of the invention. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, that is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or can readily be prepared from known starting materials. All temperatures are set forth in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight when referring to yields and all parts are by volume when referring to solvents and eluents.

General procedure for the synthesis of 1-substituted indole-4-carboxaldehydes followed by hydrazone formation:

The 1-substituted indole-4-carboxaldehydes may be prepared according to Scheme (I) below by N-alkylation of the indole-4-carboxaldehyde using various electrophilic alkylating agents that introduce the -K-D moiety as defined above, such as halides (fluorides, chlorides, bromides, iodides), methanesulfonates, toluenesulfonates or triflates.

SCHEME (I)



(I)

wherein X_L is a leaving group such as -F, -Cl, -Br, -I, $-OSO_2CH_3$, $-OSO_2$p-tolyl or $-OSO_2CF_3$ and R^1, K and D are as defined for formula (I).

According to Scheme (I) the 1-substituted indole-4-carboxaldehydes can be prepared by stirring indole-4-carboxaldehyde in a solvent such as acetone, methylethyl ketone, dimethylformamide, dioxane, tetrahydrofuran, toluene, ethylene glycol dimethyl ether, sulfolane, diethylether, dimethylsulfoxide, water or a compatible mixture of two or more of the above solvents with an equimolar amount of X_L-K-D, e.g. a substituted benzyl halide, or a carboxylic acid anhydride in the presence of 1 to 15 equivalents (preferably 1 to 5 equivalents) of a base such as sodium hydride, potassium hydride, sodium or potassium methoxide, ethoxide or *tert*-butoxide, sodium, potassium or cesium carbonate, potassium or cesium fluoride, sodium or potassium hydroxide or organic bases such as diisopropylethylamine, 2,4,6-collidine or benzyldimethyl ammonium methoxide or hydroxide. The reaction can be performed at 0°C to 150°C, preferably at 20°C to 100°C and preferably in an inert atmosphere of N_2 or Ar. When the reaction is complete the mixture is filtered, concentrated in vacuo and the resulting product is optionally purified by column chromatography on silica gel using ethyl acetate/hexane as eluent. The compound can also (when appropriate) be purified by recrystallization from a suitable solvent such as ethyl alcohol, ethyl acetate, isopropyl alcohol, water, hexane, toluene or their compatible mixture.

The resulting carboxaldehydes are then treated with the corresponding acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, dimethylsulfoxide, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid or trifluoroacetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere

of N_2 or Ar at temperatures between 0°C to 140°C, preferably between 10°C to 80°C. In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate.

Library procedure for indole alkylation:

Preparation of the sodium salt of the indole:

Indole-4-carboxaldehyde (1.45 g) was dissolved into 8.6 mL of dry dimethylformamide in a dried and cooled 100 mL 3-necked round bottom flask.

While maintaining a steady flow of nitrogen or argon through the 3-necked round bottomed flask, 1.1 equivalent of sodium hydride (0.27 g of dry 95% reagent) was transferred to the indole solution. The mixture was stirred for 15 minutes, while maintaining flow of inert gas.

Preparation of the halide solutions:

Amber glass vials (for preparing stock solutions) were dried for at least four hours at 110 °C, then were allowed to cool under an argon atmosphere in a desiccator. Halide solutions (1.0 M) were prepared in anhydrous dimethylformamide in the dried vials. Each halide solution (100 µL) was added to its corresponding well of a deep-well plate.

Alkylation of the indole sodium salt:

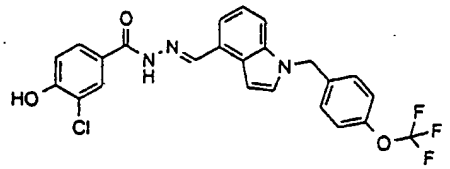
100 µL of the 1.0 M indole salt solution was quickly delivered to each halide in the deep-well plates. The plates were vortexed briefly to mix, then allowed to react for two hours.

Library procedure for hydrazone formation:

3-Substituted 4-hydroxybenzoic acid hydrazides (10 mmoles) were dissolved in 5 mL of dry dimethylsulfoxide, followed by trifluoroacetic acid (0.77 mL). The resulting solutions were diluted to final volumes of 10.0 mL. 100 µL of the 1.0 M acid hydrazide trifluoroacetic acid salt solution was added to each well of the deep-well plate. The plate was vortexed for one minute to mix, then allowed to react for 30 minutes.

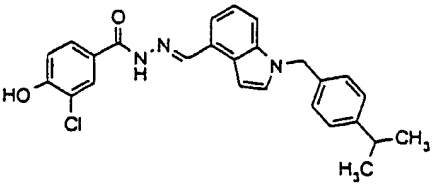
The products were purified by chromatography on silica gel with ethyl acetate/hexane eluent.

EXAMPLE 1:



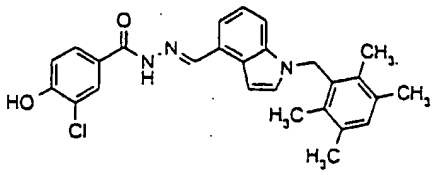
^{1}H NMR (DMSO-d_6): δ 5.54 (s, 2H), 7.07 (d, 1H), 7.20 (t, 1H), 7.26 (m, 2H), 7.31 (s, 4H), 7.58 (d, 1H), 7.68 (s, 1H), 7.80 (d, 1H), 8.01 (d, 1H), 8.66 (s, 1H), 11.98 (brd s, 1H), 11.71 (s, 1H); MS (APCI (= atmospheric pressure chemical ionization), negative): 486.0, 487.0, 488.0.

EXAMPLE 2:



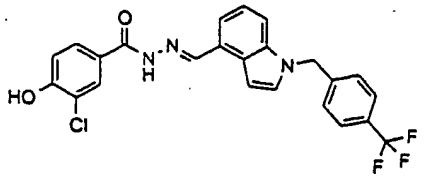
^{1}H NMR (DMSO-d_6): δ 1.13 (s, 3H), 1.15 (s, 3H), 2.83 (sept, 1H), 5.43 (s, 2H), 7.07 – 7.30 (m, 7H), 7.58 (d, 1H), 7.64 (s, 1H), 7.80 (d, 1H), 8.00 (s, 1H), 8.66 (s, 1H), 10.95 (s, 1H), 11.70 (s, 1H); MS (APCI, neg.): 444.0, 446.1.

EXAMPLE 3:



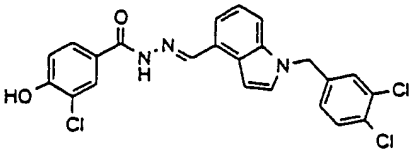
^{1}H NMR (DMSO-d_6): δ 2.08 (s, 6H), 2.21 (s, 6H), 5.37 (s, 2H), 6.77 (d, 1H), 7.04 (m, 3H), 7.26 (t, 1H), 7.35 (d, 1H), 7.77 (m, 2H), 7.97 (s, 1H), 8.67 (s, 1H), 11.00 (brd s, 1H), 11.67 (s, 1H); MS (APCI): 460.2, 461.2, 462.2.

EXAMPLE 4:



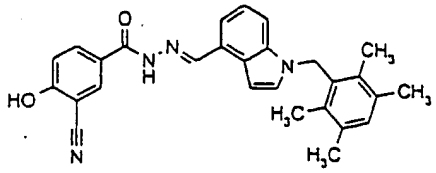
^{1}H NMR (DMSO-d_6): δ 5.61 (s, 2H), 7.04 (d, 1H), 7.17 (t, 1H), 7.30 (m, 2H), 7.34 (d, 2H), 7.52 (d, 1H), 7.67 (m, 3H), 7.79 (d, 1H), 7.80 (d, 1H), 8.66 (s, 1H), 10.97 (brd s, 1H), 11.72 (s, 1H); MS (APCI): 472.1.

EXAMPLE 5:



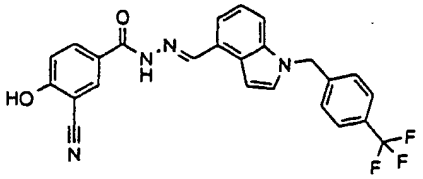
^{1}H NMR (DMSO-d_6): δ 5.51 (s, 2H), 7.01 (d, 1H), 7.12 (d, 1H), 7.22 (t, 1H), 7.27 (m, 1H), 7.30 (d, 1H), 7.49 (s, 1H), 7.58 (d, 2H), 7.68 (d, 1H), 7.80 (d, 1H), 8.01 (d, 1H), 8.66 (brd s, 1H), 10.95 (brd s, 1H), 11.72 (brd s, 1H); MS (APCI, negative): 470.9, 471.9, 473.9.

EXAMPLE 6:



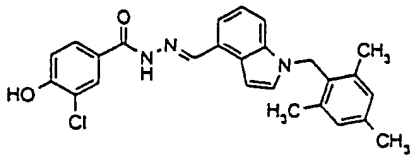
^{1}H NMR (DMSO-d_6): δ 2.08 (s, 6H), 2.21 (s, 6H), 5.37 (s, 2H), 6.78 (s, 1H), 7.05 (m, 3H), 7.26 (t, 1H), 7.34 (d, 1H), 7.76 (d, 1H), 8.01 (d, 1H), 8.19 (s, 1H), 8.64 (s, 1H), 11.68 (s, 1H). MS (APCI): 451.2, 452.2, 453.2.

EXAMPLE 7:



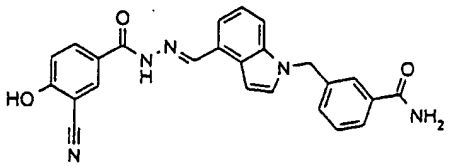
^{1}H NMR (DMSO-d_6): δ 5.61 (s, 2H), 7.12 (d, 1H), 7.18 (t, 1H), 7.27 (m, 2H), 7.34 (d, 2H), 7.54 (d, 1H), 7.66 (s, 1H), 7.69 (d, 2H), 8.08 (d, 1H), 8.25 (s, 1H), 8.64 (s, 1H), 11.78 (s, 1H); MS (APCI): 463.1, 464.2.

EXAMPLE 8:



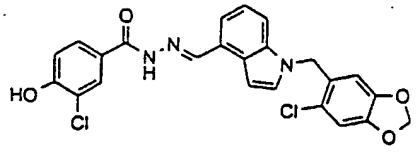
^{1}H NMR (DMSO-d_6): δ 2.17 (s, 6H), 2.26 (s, 3H), 5.33 (s, 2H), 6.88 (s, 1H), 6.94 (s, 2H), 7.07 (d, 1H), 7.11 (s, 1H), 7.24 (t, 1H), 7.32 (d, 1H), 7.69 (d, 1H), 7.78 (d, 1H), 7.99 (s, 1H), 8.66 (s, 1H), 11.00 (brd s, 1H), 11.68 (s, 1H); MS (APCI): 4461.1, 448.1.

EXAMPLE 9:



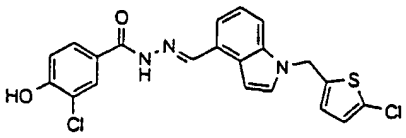
^{1}H NMR (DMSO-d_6): δ 5.53 (s, 2H), 7.14 (d, 1H), 7.20 (d, 1H), 7.25 (d, 1H), 7.30 (d, 1H), 7.41 (t, 1H), 7.57 (d, 1H), 7.67 (d, 1H), 7.75 (d, 1H), 7.79 (s, 1H), 7.97 (s, 1H), 8.10 (d, 1H), 8.26 (s, 1H), 8.65 (s, 1H), 11.77 (s, 1H); MS (APCI, negative): 436.1, 437.1.

EXAMPLE 10:



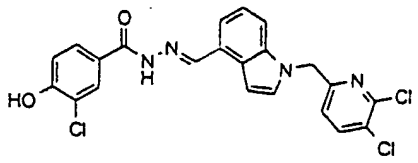
^{1}H NMR (DMSO-d_6): δ 5.45 (s, 2H), 6.03 (s, 2H), 6.37 (s, 1H), 7.08 (d, 1H), 7.15 (s, 1H), 7.22 (t, 1H), 7.25 (d, 1H), 7.32 (d, 1H), 7.53 (s, 1H), 7.56 (m, 1H) ,7.79 (d, 1H), 8.00 (s, 1H), 8.67 (s, 1H), 10.97 (brd s, 1H), 11.73 (brd s, 1H); MS (APCI, negative): 480.0, 481.0, 482.0.

EXAMPLE 11:



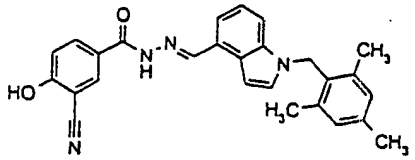
^{1}H NMR (DMSO-d_6): δ 5.60 (s, 2H), 6.58 (d, 1H), 6.88 (d, 1H), 6.98 (d, 1H), 7.06 (d, 1H), 7.53 (d, 1H), 7.64 (s, 2H), 7.77 (dd, 1H), 7.85 (s, 1H), 7.98 (d, 1H), 8.49 (s, 1H), 10.94 (brd s, 1H), 11.60 (s, 1H); MS (APCI, negative): 441.9, 442.9, 443.9.

EXAMPLE 12:



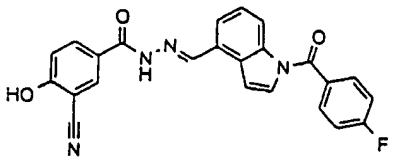
^{1}H NMR (DMSO-d_6): δ 5.56 (s, 2H), 7.08 (d, 1H), 7.22 (t, 1H), 7.27-7.32 (m, 2H), 7.66 (d, 1H), 7.72 (s, 1H), 7.80 (dd, 1H), 7.99 (t, 2H), 8.33 (d, 1H), 8.65 (s, 1H), 10.86 (brd s, 1H), 11.72 (s, 1H); MS (APCI): 473.0, 475.0.

EXAMPLE 13:



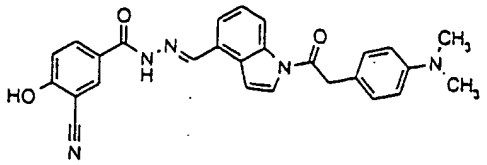
^{1}H NMR (DMSO-d_6): δ 2.17 (s, 6H), 2.25 (s, 3H), 5.33 (s, 2H), 6.88 (s, 1H), 6.93 (s, 2H), 7.08 (s, 1H), 7.11 (s, 1H), 7.22 (t, 1H), 7.28 (d, 1H), 7.70 (d, 1H), 8.05 (d, 1H), 8.23 (s, 1H), 8.65 (s, 1H), 11.72 (brd s, 1H); MS (APCI): 437.2, 438.2, 439.2.

EXAMPLE 14:



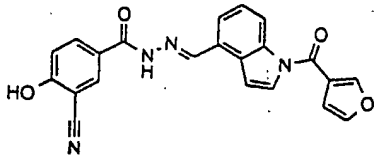
^{1}H NMR (DMSO-d_6): δ 6.88 (d, 1H), 7.45 (t, 4H), 7.55 (d, 2H), 7.85-7.90 (m, 2H), 7.94 (d, 1H), 8.15 (s, 1H), 8.32 (d, 1H), 8.66 (brd s, 1H), 11.77 (s, 1H); MS (APCI): 427.1, 428.1.

EXAMPLE 15:



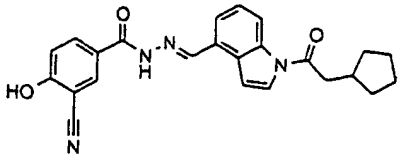
^{1}H NMR (DMSO-d_6): δ 2.85 (s, 6H), 4.28 (s, 2H), 6.68 (d, 2H), 7.06 (d, 1H), 7.18 (d, 1H), 7.39 (t, 1H), 7.47 – 7.51 (m, 2H), 8.05 (d, 1H), 8.21 (s, 1H), 8.40 (d, 1H), 8.62 (s, 1H), 11.82 (s, 1H); MS (APCI): 466.2, 467.3.

EXAMPLE 16:



^{1}H NMR (DMSO-d_6): δ 7.01 (s, 1H), 7.10 (d, 1H), 7.45 (t, 1H), 7.55 (m, 2H), 7.95 (s, 1H), 7.98 (d, 1H), 8.10 (d, 1H), 8.24 (s, 1H),8.39 (d, 1H), 8.53 (s, 1H), 8.65 (s, 1H), 11.86 (s, 1H); MS (APCI, neg.): 397.1, 398.1.

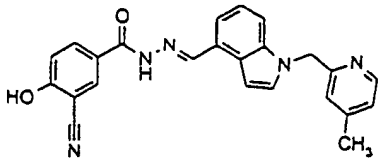
EXAMPLE 17:



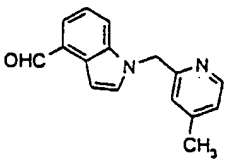
^{1}H NMR (DMSO-d_6): δ 1.20-1.27 (m, 2H), 1.50-1.65 (m, 5H), 1.80-1.86 (m, 2H), 2.33 (sept, 1H), 3.09 (d, 2H), 7.05 (d, 1H), 7.39 (t, 1H), 7.49 (m, 3H), 8.02 (d, 1H), 8.07 (s, 1H), 8.21 (s, 1H), 8.44 (d, 1H), 8.63 (s, 1H), 11.82 (s, 1H); MS (APCI): 415.2, 416.2.

EXAMPLE 18:

3-Cyano-4-hydroxybenzoic acid {1-[(4-methyl-2-pyridinyl)methyl]-indol-4-yl}methylidene hydrazide



4-Formyl-1-[(4-methyl-2-pyridinyl)methyl]-indole:



The compound was prepared from 4-formylindole and 2-chloromethyl-4-methyl pyridine [prep. from 2,4-lutidine acc. G. E. Jeromin et al. Chem. Ber. 120, 1987, 640-451] following the general procedure for alkylation of indoles.

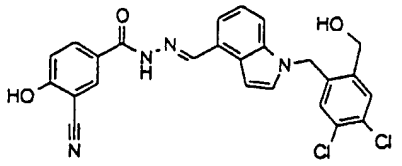
^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H), 5.48 (s, 2H), 6.54 (s, 1H), 7.01 (d, J = 4.8 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.39 (d, J=3.0 Hz, 1H), 7.43 (d, J = 3.0 Hz, 1H), 8.45 (s, 1H), 10.27 (s, 1H).

The title compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 4-formyl-1-[(4-methyl-2-pyridinyl)methyl]-indole and 3-cyano-4-hydroxy benzoic acid hydrazide.

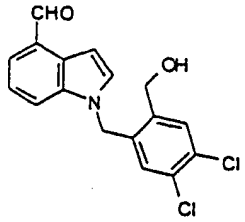
^{1}H NMR (DMSO-d_6): δ 1.53 (s, 3H), 5.50 (s, 2H), 6.86 (s, 1H), 7.10 (d, J = 5.0 Hz, 1H), 7.13 (d, J=8.7 Hz, 1H), 7.17 (dd, J =J'=7.8 Hz, 1 H), 7.24 (d, J = 2.7 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 2.7 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 8.25 (s, 1H), 8.37 (d, J = 4.9 Hz, 1H), 11.76 (s, 2H); MS (APCI, pos.): 410.

EXAMPLE 19:

3-Cyano-4-hydroxybenzoic acid {1-[(4,5-dichloro-2-hydroxymethyl)benzyl]-indol-4-yl}methylidene hydrazide



4-Formyl-1-(4,5-dichloro-2-hydroxymethylbenzyl)-indole:



This compound was prepared from 4-formylindole and 4,5-dichloro-2-tetrahydropyranyloxy benzylchloride [prep. from 1,2-dihydroxymethyl-4,5-dichloro benzene acc. W. Y. Lee et al. J. Org. Chem. 57, 1992, 4074-4079] following the general procedure for alkylation of indoles. After treatment of the product with 1N HCl in tetrahydrofuran, 4-formyl-1-(4,5-dichloro-2-hydroxymethylbenzyl)indole was obtained.

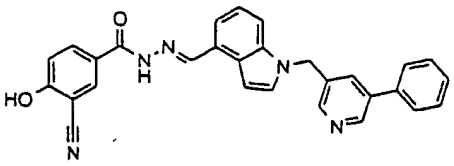
^{1}H NMR ($CDCl_3$): δ 4.65 (s, 2H), 5.45 (s, 2H), 6.81 (s, 1H), 7.26 (s, 1 H), 7.27 (d, J = 3.4 H8 Hz, 1 H), 7.32 (d, J =7.9 Hz, 1 H), 7.36 (d, J =3.8 Hz, 1 H), 7.51 (d, J =6.8 Hz, 1 H), 7.52 (s, 1H), 7.66 (d, J = 7.2 Hz, 1H), 10.25 (s, 1H).

The title compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 4-formyl-1-(4.5-dichloro-2-hydroxy-methylbenzyl)-indole and 3-cyano-4-hydroxy benzoic acid hydrazide.

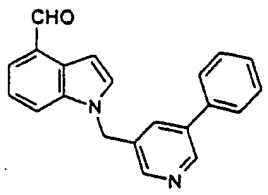
^{1}H NMR (DMSO-d_6): δ 4.55 (s, 2H), 5.51 (s, 3H), 6.60 (s, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.20 (m, 1H), 7.30 (m, 2 H), 7.49 (d, J =8.0 Hz, 1H), 7.55 (s, 1H), 7.66 (s, 1H), 8.8 (d, J=8.5 Hz, 1H), 8.26 (s, 1H), 8.65 (s, 1H), 11.79 (s, 2H); MS (APCI, pos.): 493.

EXAMPLE 20:

3-Cyano-4-hydroxybenzoic acid {1-[(5-phenyl-3-pyridinyl)methyl]-indol-4-yl}methylidene hydrazide



4-Formyl-1-[(5-phenyl-3-pyridinyl)methyl]-indole:



The compound was prepared from 4-formylindole and 3-chloromethyl-5-phenyl pyridine [prep. from 5-methyl-3-phenylpyridine by chlorination with NCS/AIBN] following the general procedure for alkylation of indoles.

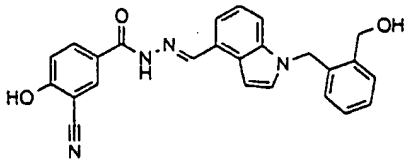
^{1}H NMR ($CDCl_3$): δ 5.49 (s, 2 H), 7.40 (m, 2 H), 7.43 – 7.46 (m, 3H), 7.50 (m, 1H), 7.66 (dd, J = 0.8, 7.2 Hz, 1H), 7.67 (s, 1 H), 8.78 (s, 1H), 10.26 (s, 1H).

The title compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 4-formyl-1-[(5-phenyl-3-pyridinyl)methyl]-indole and 3-cyano-4-hydroxy benzoic acid hydrazide.

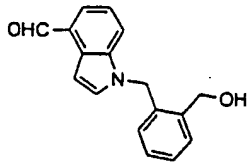
^{1}H NMR (DMSO-d_6): δ 5.61 (s, 2 H), 6.97 (d, 1H), 7.20 (dd, 1 H), 7.27 (dd, 1H), 7.37–7.47 (m, 3H), 7.59-7.66 (m, 3H), 7.74 (d, 1H), 7.90 (s, 1H), 7.97 (d, 1H), 8.14 (d, 1H), 8.42 (s, 1H), 8.60 (s, 1H), 8.73 (s, 1H), 11.67 (s, 2H); MS (APCI, pos.): 472.

EXAMPLE 21:

3-Cyano-4-hydroxybenzoic acid {1-[(2-hydroxymethyl)benzyl]-indol-4-yl}methylidene hydrazide



4-Formyl-1-(2-hydroxymethylbenzyl)-indole:



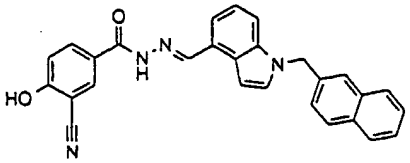
This compound was prepared from 4-formylindole and 2-tetrahydropyranyloxy benzylchloride [prep. from 1,2-benzene dimethanol acc. W. Y. Lee et al. J. Org. Chem. 57, 1992, 4074-4079] following the general procedure for alkylation of indoles. After treatment of the product with 1N HCl in tetrahydrofuran, 4-formyl-1-(2-hydroxymethylbenzyl)-indole was obtained.

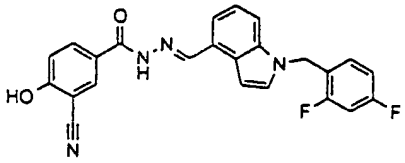
^{1}H NMR ($CDCl_3$): δ 4.72 (s, 2H), 5.53 (s, 2H), 6.73 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.27 – 7.35 (m, 4H), 7.39 (d, J = 7.1 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 10.24 (s, 1H).

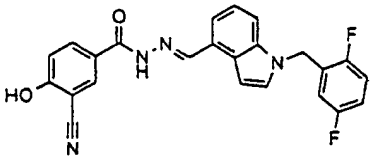
The title compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 4-formyl-1-(2-hydroxymethylbenzyl)-indole and 3-cyano-4-hydroxy benzoic acid hydrazide.

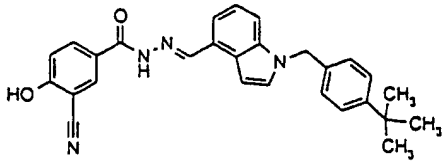
^{1}H NMR (DMSO-d_6): δ 4.60 (s, 1H), 5.30 (s, 1H), 5.55 (s, 2 H), 6.47 (d, J = 7.5 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.20–7.32 (m, 3H), 7.43 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.53 (d, J = 2.5 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 8.26 (s, 1H), 8.65 (s, 1H), 11.78 (s, 2H).

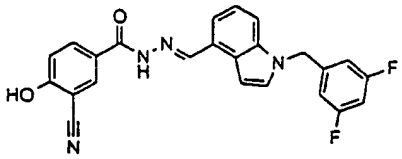
The following preferred group of compounds of the formula (I) were made according to the above library procedures:

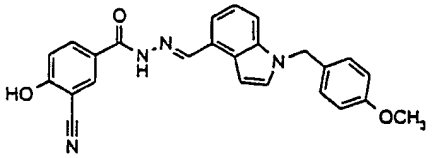


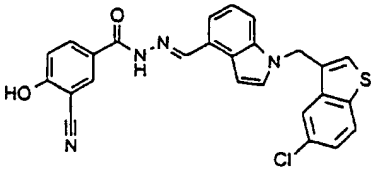


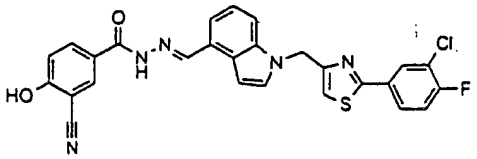


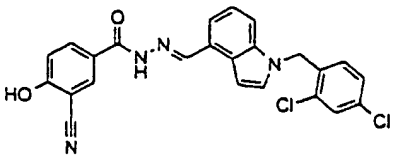


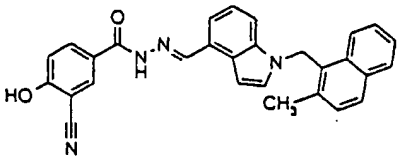


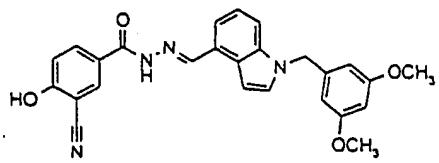


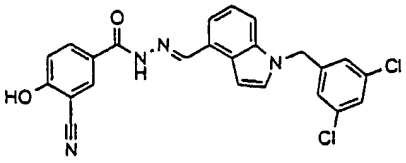


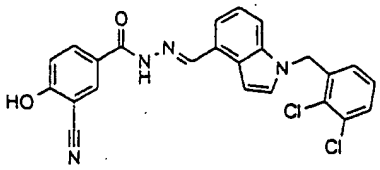


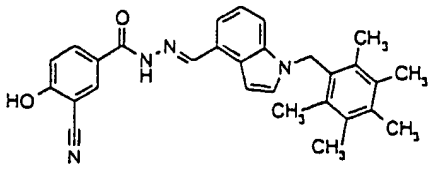


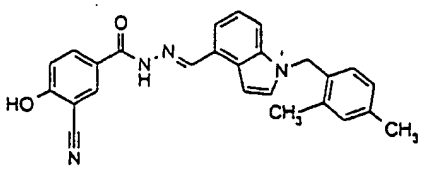


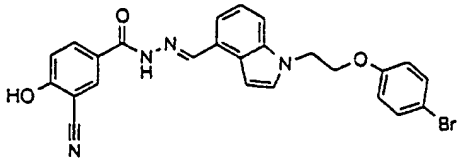


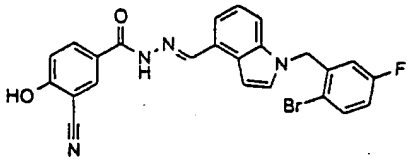


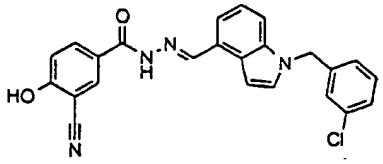


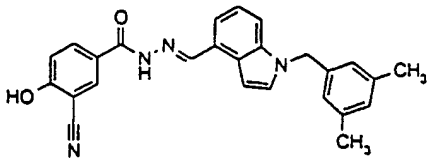


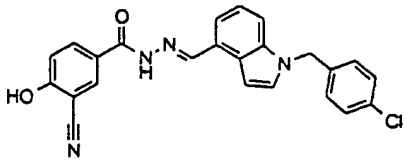


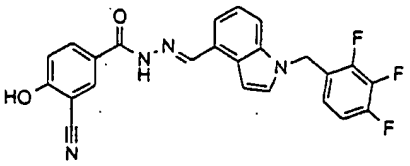


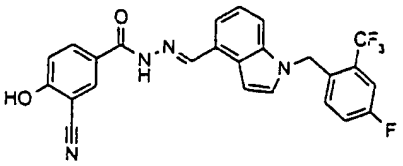


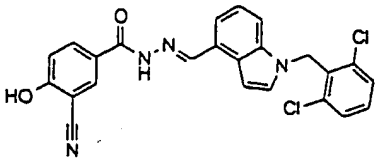


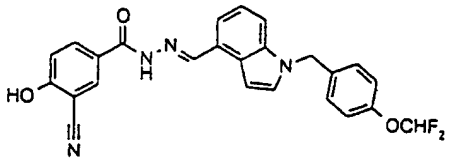


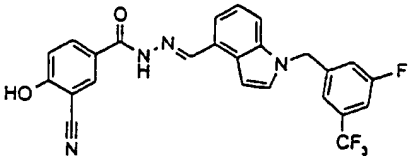


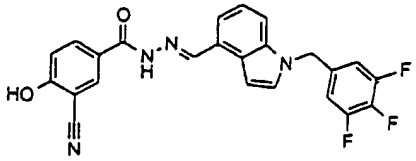


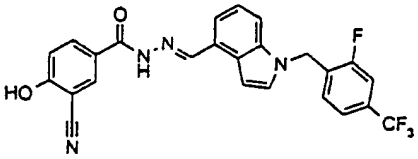


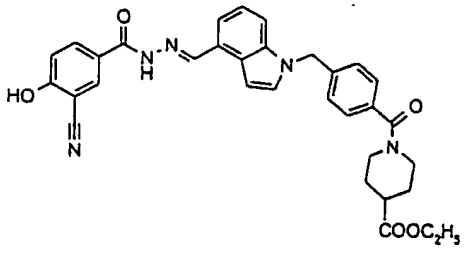


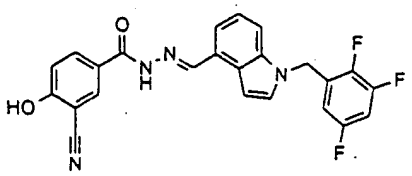


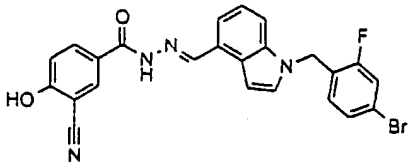


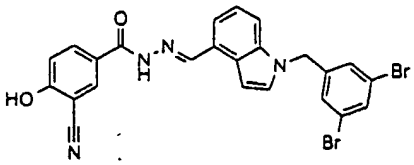


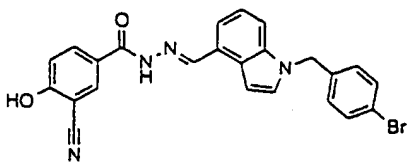


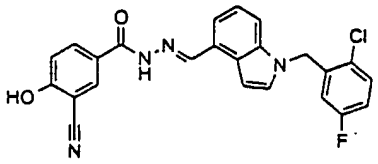


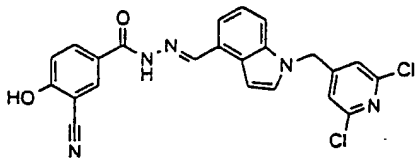


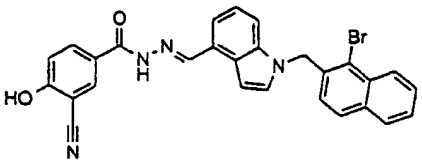


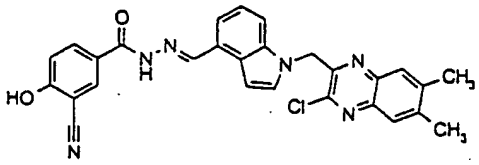


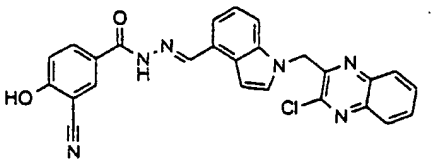


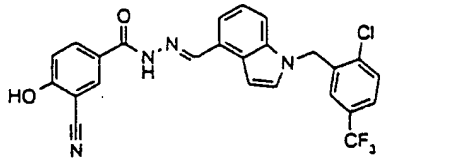






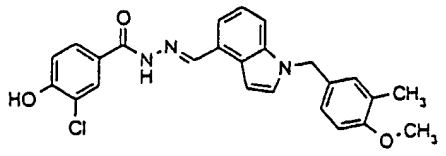


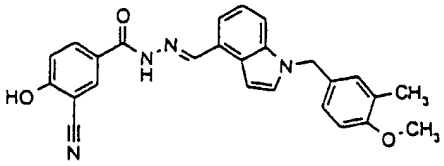


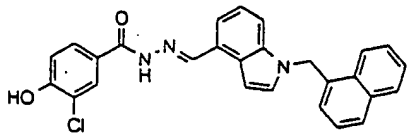


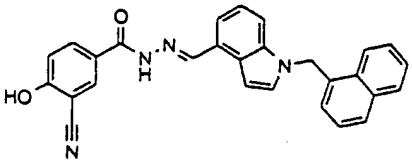
5

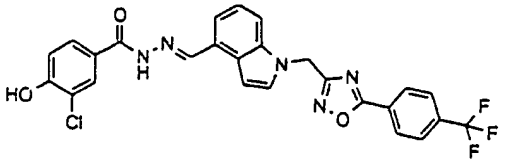
A further preferred embodiment of the invention are the following compounds of the formula (I):

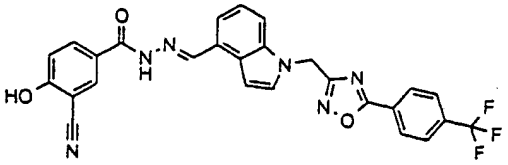


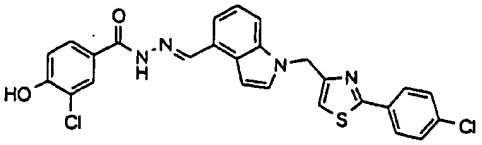


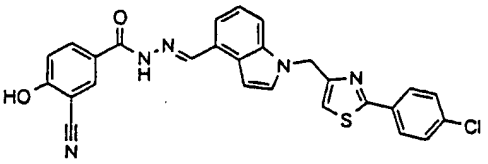


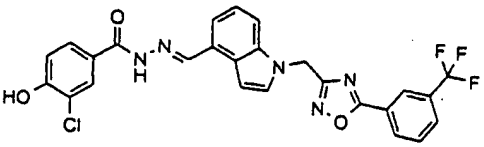


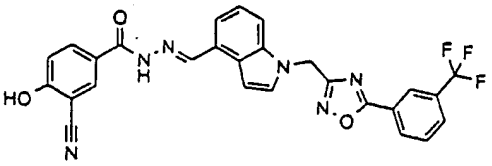


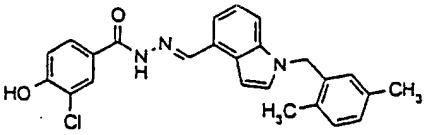


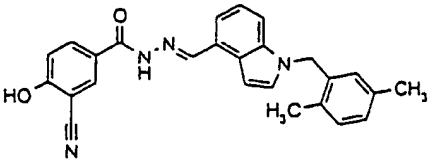


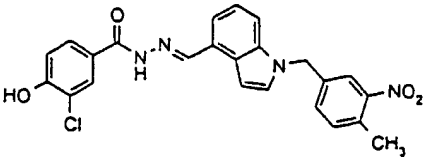


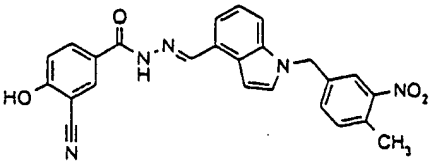


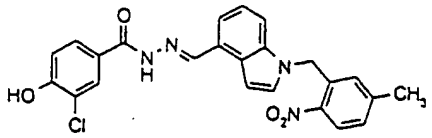
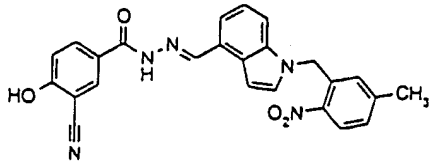
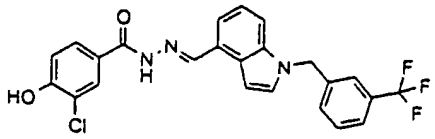
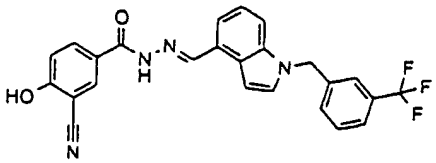
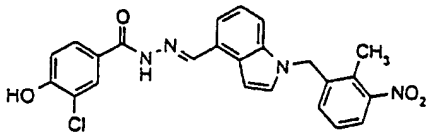
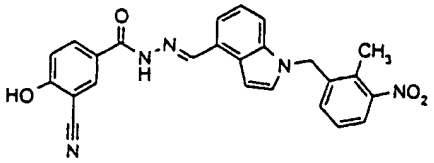
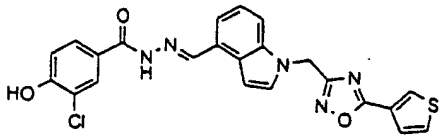
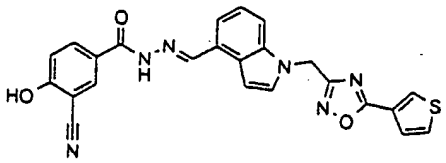
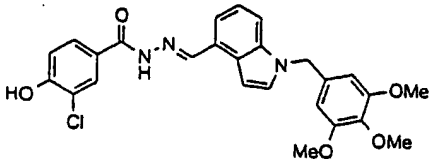
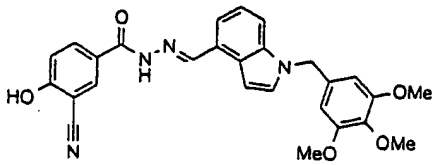
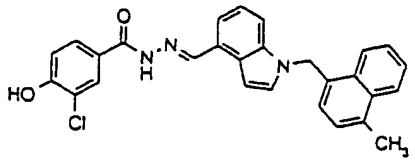
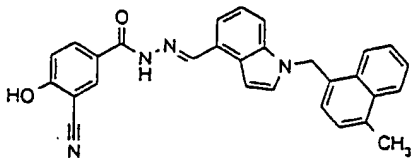
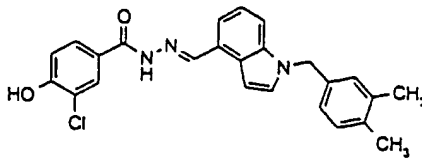
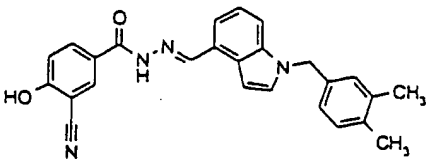
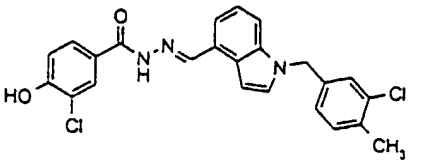
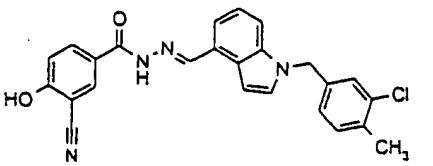


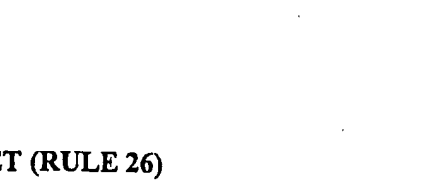


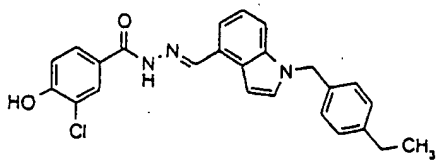


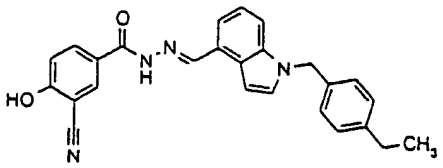


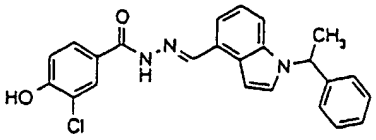


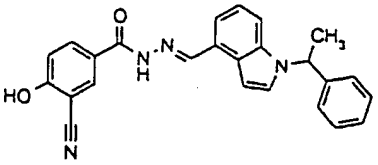

















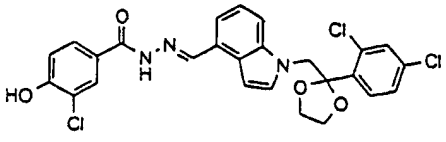


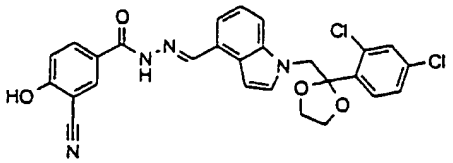


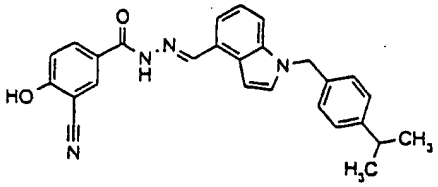


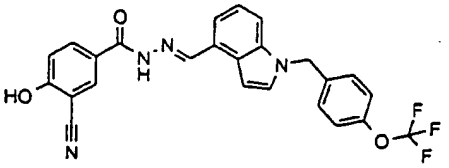


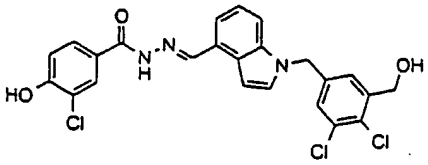


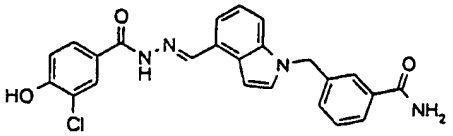


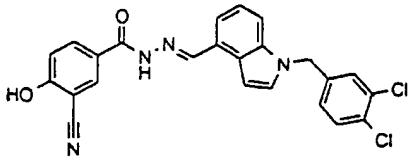


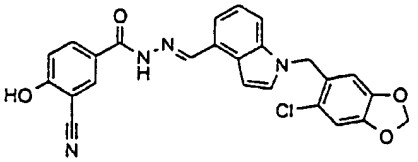


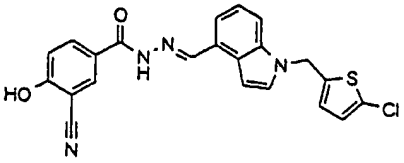


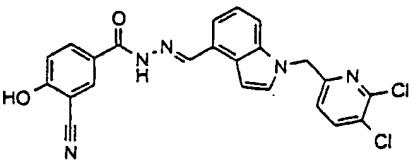


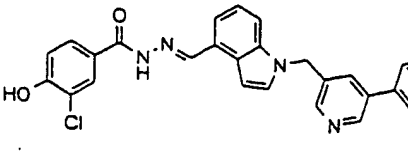


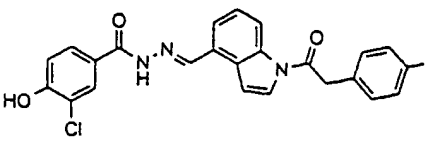


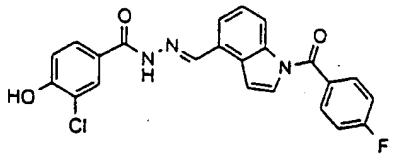


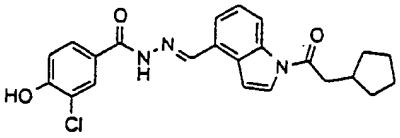


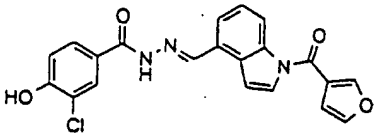




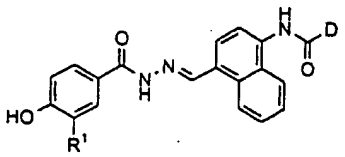








In a further aspect the invention relates to amides of 1-naphthylamine of the general formula (II):

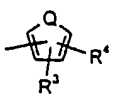


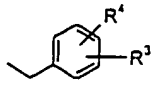
(II)

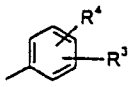
wherein

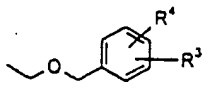
R^1 is chloro, fluoro, nitro or cyano; and

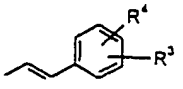
D is C_{1-6}-alkyl, C_{3-8}-cycloalkyl,



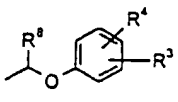








or



;

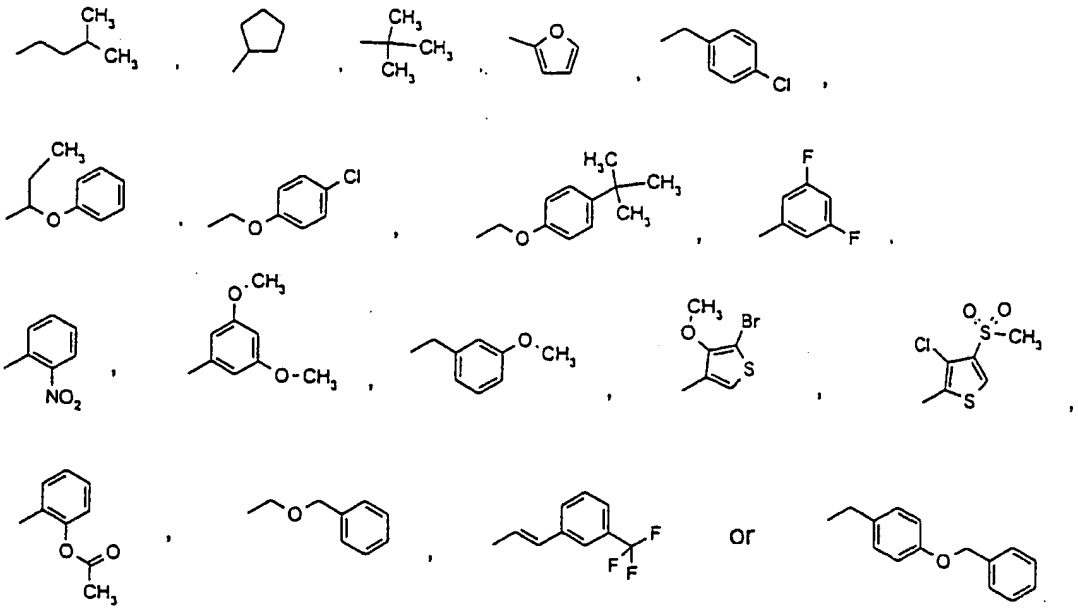
wherein R^3 and R^4 independently are hydrogen, halogen, cyano, nitro, acetoxy, C_{1-6}-alkoxy, benzyloxy, trifluoromethyl, methylsulfonyl or C_{1-6}-alkyl;

Q is -O- or -S-; and

R^8 is hydrogen or C_{1-6}-alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a preferred embodiment D is



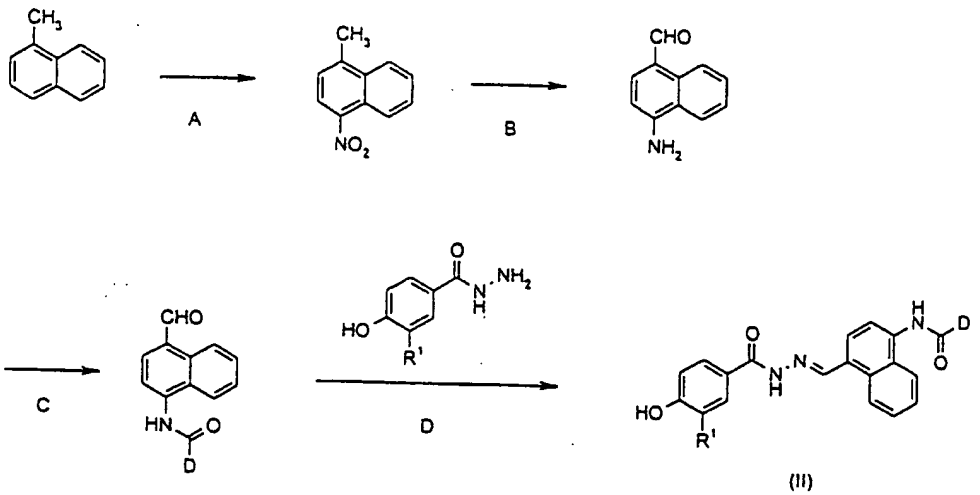
In another preferred embodiment R^1 is chloro.

More preferred R^1 is cyano.

The present invention is further illustrated by the following representative examples which are, however, not intended to limit the scope of the invention in any way.

The compounds of the general formula (II) may be prepared according to the general procedure outlined in the below reaction Scheme (II):

SCHEME (II)



Step A: 4-Nitro-1-methylnaphthalene.

To a cold (0°C) suspension of 1-methylnaphthalene (5 g) in HNO_3 was added H_2SO_4 (5 mL) dropwise. After stirring the reaction for one hour, the solution was diluted with ethyl acetate and washed with water (3x), aqueous saturated $NaHCO_3$ (2x) and brine, dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography using ethyl acetate:hexane (5:95) and recrystallized from methanol to give yellow needles.

^1H NMR ($CDCl_3$): δ 2.79 (s, 3H), 7.38 (d, 1H), 7.65-7.73 (m, 2H), 8.10 (d, 1H), 8.14 (d, 1H), 8.61 (d, 1H).

Step B: 4-Aminonaphthaldehyde.

To a stirring boiling solution of sulfur (3.7 g) in 12% aqueous NaOH (50 mL) was added a solution of 4-nitro-1-methylnaphthalene (8 g) in ethanol (50 mL). After refluxing the solution for one hour, the reaction was diluted with 500 mL of ethyl acetate and washed with water and brine, dried over $MgSO_4$, and concentrated. The product was purified via silica gel column chromatography using ethyl acetate:hexane (5:95 to 10:90). The product (2.54 g, 34%) was stored at -78°C.

^1H NMR (DMSO-d_6): δ 6.55 (d, 1H), 6.95 (brd s, 2H), 7.25 (t, 1H), 7.45 (t, 1H), 7.60 (d, 1H), 8.05 (d, 1H), 9.10 (d, 1H), 9.68 (s, 1H).

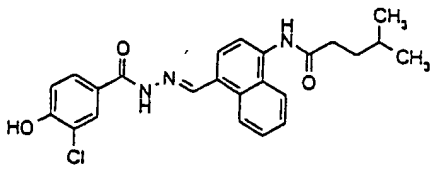
Step C: General procedure for the acylation of 4-aminonaphthaldehyde with acid chlorides.
To a solution of 4-aminonaphthaldehyde, diisopropylethylamine (1.1 eq), and 4-dimethylaminopyridine (1.1 eq) in minimum volume of anhydrous dimethylformamide was added the desired acid chloride (1.1 eq). After stirring the mixture overnight, the mixture was diluted with ethyl acetate and washed with 1N HCl (2x), water, aqueous $NaHCO_3$ (3x), water and brine, dried over $MgSO_4$, and concentrated. The acylated products were purified by silica gel column chromatography using ethyl acetate/hexane. The yield ranged from 50 - 90% yield.

Step D: General procedure for the preparation of hydrazones.
Hydrazones were prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of the appropriate 3-substituted 4-hydroxybenzoic acid hydrazide and the above acylated aldehydes.

Combinatorial Format: General procedure for the formation of acylated hydrazones in parallel synthesis format.
To a solution of 4-aminonaphthylmethyl 3-substituted hydroxybenzoic acid hydrazide (50 µL, 0.2 M) was added a solution of the desired acid chloride (55 µL, 0.2 M), a solution of diisopropylethylamine (55 µL, 0.2 M), and a solution of 4-dimethylaminopyridine (55 µL, 0.2M). The reaction mixtures were left under stirring overnight to give the desired products. The products were purified by HPLC equipped with a reverse phase column. All solutions were prepared using anhydrous dimethylformamide.

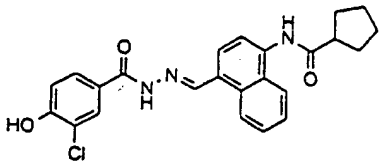
Examples of products of the formula (II):

EXAMPLE 22:



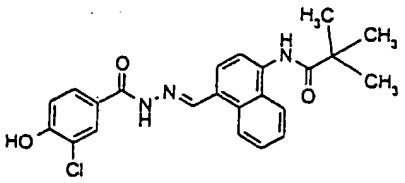
^{1}H NMR (DMSO-d_6): δ 0.96 (d, 6H), 1.55-1.68 (m, 4H), 2.55 (m, 1H), 7.10 (d, 1H), 7.63-7.71 (m, 2H), 7.80 (d, 1H), 7.89 (qt, 2H), 8.02 (s, 1H), 8.20 (d, 1H), 8.91 (d, 1H), 9.04 (s, 1H), 10.04 (s, 1H), 10.99 (s, 1H), 11.78 (s, 1H); MS (APCI): 438.1.

EXAMPLE 23:



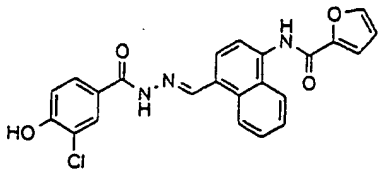
^{1}H NMR (DMSO-d_6): δ 1.61 (m, 2H), 1.71 (m 2H), 1.82 (m, 2H), 1.90 (m, 2H), 3.06 (quintet, 1H), 7.10 (d, 1H), 7.65 (quintet, 2H), 7.83 (qt, 2H), 7.90 (d, 1H), 8.02 (s, 1H), 8.18 (d, 1H), 8.90 (d, 1H), 9.04 (s, 1H), 10.01 (s, 1H), 10.99 (s, 1H), 11.78 (s, 1H); MS (APCI): 436.1, 438.2.

EXAMPLE 24:



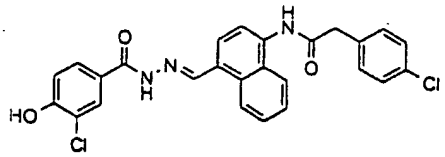
^{1}H NMR (DMSO-d_6): δ 1.34 (s, 9H), 7.17 (d, 1H), 7.54 (d, 1H), 7.66 (quintet, 2H), 7.88 (d, 1H), 7.96 (t, 2H), 8.06 (s, 1H), 8.83 (d, 1H), 9.27 (s, 1H), 9.63 (s, 1H), 11.18 (brd s, 1H), 12.09 (s, 1H); MS (APCI): 424.0.

EXAMPLE 25:



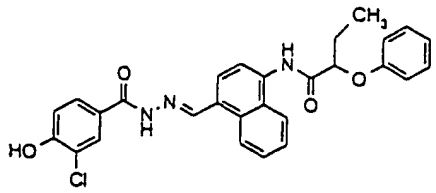
^{1}H NMR (DMSO-d_6): δ 6.76 (s, 1H), 7.11 (d, 1H), 7.44 (d, 1H), 7.65-7.74 (m, 3H), 7.82 (d, 1H), 8.02 (m, 3H), 8.07 (d, 1H), 8.90 (d, 1H), 9.09 (s, 1H), 10.49 (s, 1H), 11.01 (s, 1H), 11.84 (s, 1H); MS (APCI): 434.0, 436.0.

EXAMPLE 26:



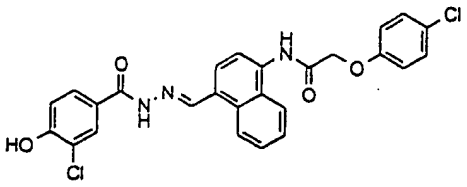
^{1}H NMR (DMSO-d_6): δ 3.87 (s, 2H), 7.08 (d, 1H), 7.44 (s, 4H), 7.66 (m, 2H), 7.80-7.89 (m, 3H), 8.01 (s, 1H), 8.20 (d, 1H), 8.90 (d, 1H), 9.04 (s, 1H), 10.32 (s, 1H), 11.99 (s, 1H), 11.78 (s, 1H); MS (APCI): 490.3, 492.1, 493.1.

EXAMPLE 27:



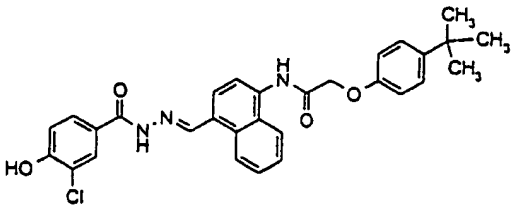
^{1}H NMR (DMSO-d_6): δ 1.12 (s, 3H), 2.01 (quintet, 1H), 5.00 (t, 1H), 7.00 (t, 1H), 7.10 (m, 3H), 7.40 (t, 2H), 7.60 (t, 1H), 7.70 (t, 1H), 7.72 (d, 1H), 7.80 (d, 1H), 7.90 (d, 1H), 7.95 (d, 1H), 8.00 (s, 1H), 8.80 (d, 1H), 9.10 (s, 1H), 10.40 (s, 1H),10.90 (s, 1H), 11.80 (s, 1H); MS (APCI): 502.2, 503.2, 504.2.

EXAMPLE 28:



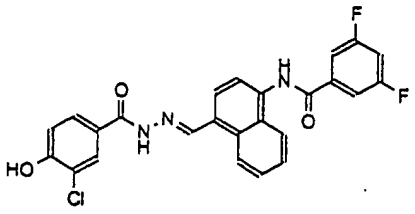
^{1}H NMR (DMSO-d_6): δ 4.93 (s, 2H), 7.10 (d, 3H), 7.40 (d, 2H), 7.67 (t, 1H), 7.70 (t, 1H), 7.82 (d, 2H), 7.94 (d, 1H), 8.02 (s, 1H), 8.11 (d, 1H), 8.90 (d, 1H), 9.06 (s, 1H), 10.33 (s, 1H), 11.02 (s, 1H), 11.82 (s, 1H); MS (APCI): 508.1, 509.1, 510.1.

EXAMPLE 29:



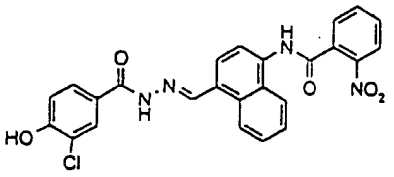
^{1}H NMR (DMSO-d_6): δ 1.27 (s, 9H), 4.88 (s, 2H), 6.99 (d, 2H), 7.10 (d, 1H), 7.35 (d, 2H), 7.61 (t, 1H), 7.69 (t, 1H), 7.81 (d, 2H), 7.93 (d, 1H), 8.02 (s, 1H), 8.06 (d, 1H), 8.90 (d, 1H), 9.09 (s, 1H), 10.30 (s, 1H), 11.04 (brd s, 1H), 11.86 (s, 1H); MS (APCI): 530.2, 532.2.

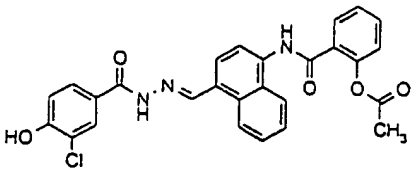
EXAMPLE 30:

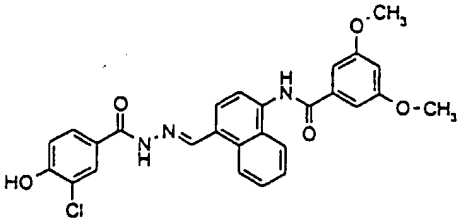


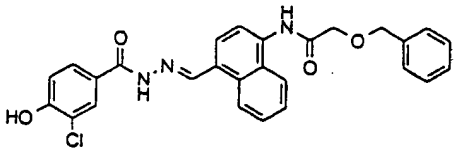
^{1}H NMR (DMSO-d_6): δ 7.00 (d, 1H), 7.55-7.75 (m, 2H), 7.80 (d, 2H), 7.85 (d, 3H), 8.00 (d, 1H), 8.10 (s, 1H), 8.20 (d, 1H), 8.90 (d, 1H), 9.20 (s, 1H), 10.70 (s, 1H), 11.00 (s, 1H), 11.80 (s, 1H); MS (APCI): 480.1.

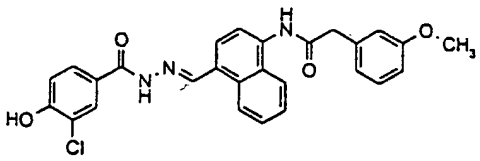
The following compounds of the formula (II) may also be prepared using the above mentioned synthesis methodologies:

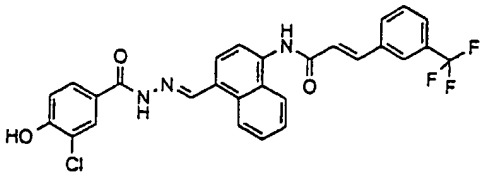


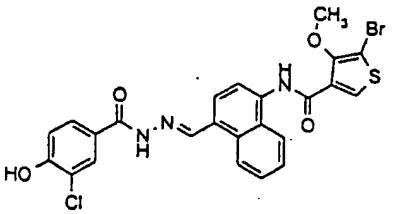


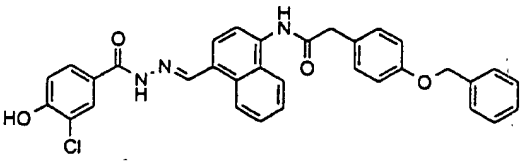


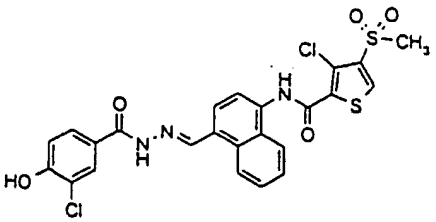


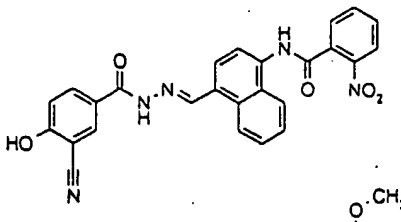


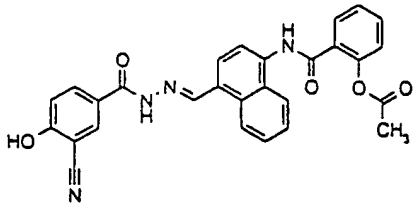


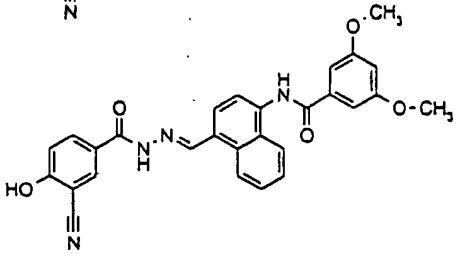


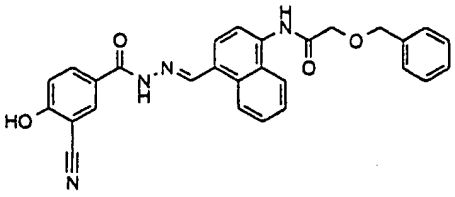


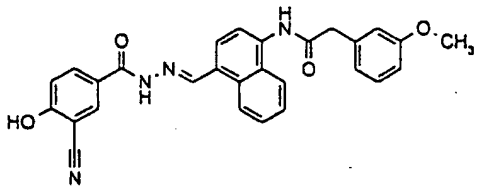


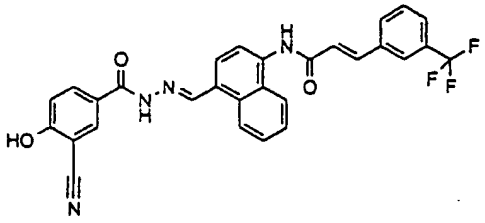


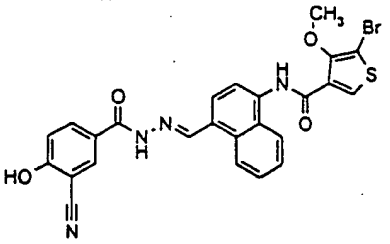


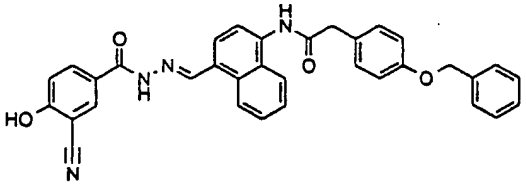


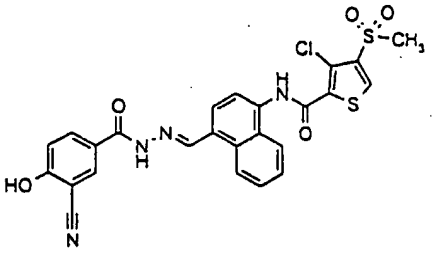


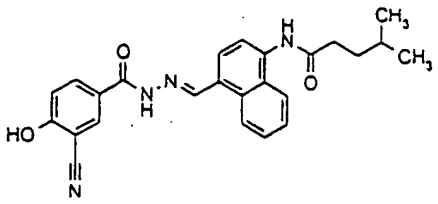


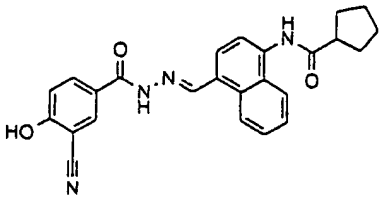


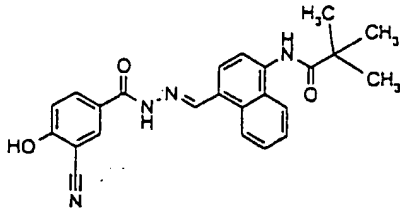


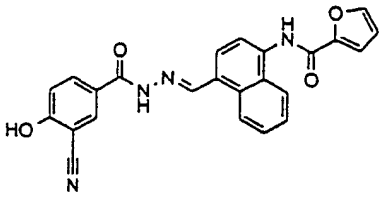


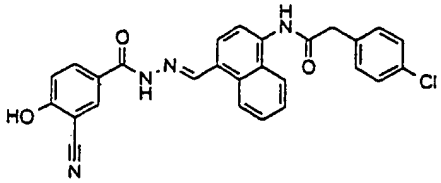


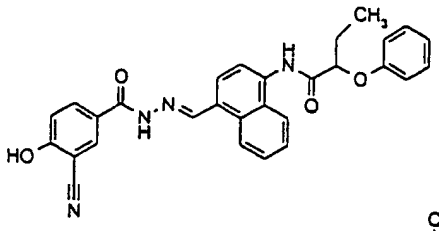


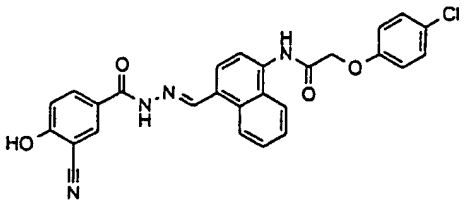


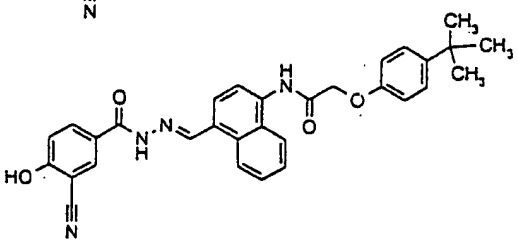


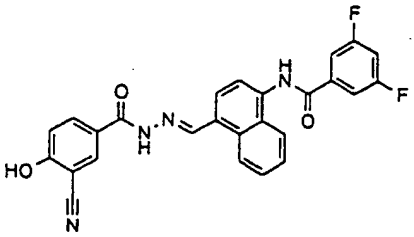












In a further aspect the invention relates to the following compounds:

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(2-trifluoromethyl-phenyl)acetamide;

3-phenylpropynoic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxy-phenyl}amide;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-chlorophenyl)-acetamide;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3-chloro-phenyl)-acetamide;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-trifluoromethyl-phenylsulfanyl)acetamide;

5-methoxybenzofuran-2-carboxylic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl)amide;

2-benzo[b]thiophen-3-yl-N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxy-phenyl}acetamide;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3,4-difluoro-phenyl)acetamide;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-chlorophenyl-sulfanyl)acetamide;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-3-(4-chlorophenyl)-propionamide;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-3-(4-cyanophenoxy)-acetamide;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(2-trifluoromethyl-phenyl)acetamide;

3-phenylpropynoic acid {4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxy-phenyl}amide;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-chlorophenyl)-acetamide;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3-chlorophenyl)-acetamide;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-trifluoromethyl-phenylsulfanyl)acetamide;

5-methoxybenzofuran-2-carboxylic acid {4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl)amide;

2-benzo[b]thiophen-3-yl-N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxy-phenyl)acetamide;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3,4-difluoro-phenyl)acetamide;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3-trifluoromethyl-phenyl)acetamide;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-3-(4-trifluoromethyl-phenyl)propionamide;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-chlorophenyl-sulfanyl)acetamide;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-3-(4-chlorophenyl)-propionamide;

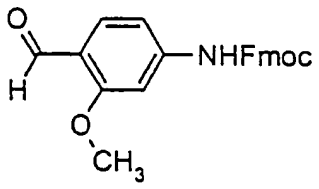
N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-3-(4-cyanophenoxy)-acetamide;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

General procedure for synthesis of the compounds

Preparation of [Building block 2]

(4-Formyl-3-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester:



Methyl 4-amino-2-methoxybenzoate (14.7 g, 7.3 mmol) and Fmoc-OSu (26.1 g, 77.3 mmol) were stirred in a mixture of acetonitrile and water (1:1, 320 mL) at reflux for 16 hr. The reaction mixture was concentrated to half the volume and the precipitate isolated by filtration. The isolated solid was dissolved in ethyl acetate (300 mL) and washed with 0.4 N hydrochloric acid (200 mL), 0.2 N hydrochloric acid (200 mL), water (200 mL) and a 20% saturated solution of sodium chloride (200 mL). After drying (magnesium sulphate) the organic phase was concentrated in vacuo, and the solid residue was washed with methanol and dried.

The crude product (12 g) was dissolved in dichloromethane (1 L) under nitrogen and a solution of diisobutylaluminium hydride (90 mL, 1.2 M in toluene) was dropwise added at 0-5°C. The reaction mixture was stirred at 20°C for 16 hr and quenched by dropwise addition of water (58 mL) at 0-5°C. The reaction mixture was stirred at 20°C for 3 hr and filtered. The filtrate was concentrated in vacuo. The crude product (6.8 g) was suspended in dichloromethane (400 mL) and manganese dioxide (15.6 g, 180 mmol) was added. The mixture was stirred for 16 hr at 20°C and filtered. The filtrate was concentrated in vacuo to give 5.1 g of the title compound.

M.p. 187-188°C.

HPLC-MS (METHOD A): R_t = 15.1 min; m/z= 374.

Micro analysis: Calculated: C, 73.98; H, 5.13; N, 3.75%
Found: C, 73.44; H, 5.20; N, 3.56%.

HPLC-MS (METHOD A):

The following instrumentation is used:

- Sciex API 100 Single quadropole mass spectrometer
- Perkin Elmer Series 200 Quard pump
- Perkin Elmer Series 200 autosampler
- Applied Biosystems 785A UV detector
- Sedex 55 evaporative light scattering detector
- A Valco column switch with a Valco actuator controlled by timed events from the pump.

The instrument control and data acquisition is done by the Sciex Sample control software running on a Macintosh PowerPC 7200 computer.

The HPLC pump is connected to four eluent reservoirs containing:

A: acetonitrile
B: water
C: 0.5 % trifluoroacetic acid in water
D: 0.02 M ammonium acetate

The requirements for samples are that they contain approximately 500 µg/mL of the compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, tetrahydrofuran, water and mixtures thereof. (High concentrations of strongly eluting solvents will interfere with the chromatography at low acetonitrile concentration.)

The analysis is performed at room temperature by injecting 20 µL of the sample solution on the column which is eluted with a gradient of acetonitrile in either 0.05% trifluoroacetic acid or 0.002 M ammonium acetate. Depending on the analysis method varying elution conditions are used.

The eluate from the column is passed through a flow splitting T-connector which passes approximately 20 µl/min (1/50) through approx. 1 m. 75 µ fused silica capillary to the API interface of API 100 spectrometer.

The remaining 1.48 mL/min (49/50) is passed through the UV detector and to the ELS detector.

During the LC-analysis the detection data are acquired concurrently from mass spectrometer, UV detector and ELS detector.

The LC conditions, detector settings and mass spectrometer settings used for the different methods are given in the following tables.

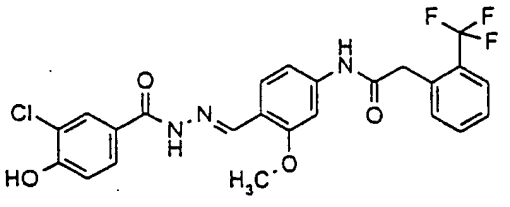
Method	h8 LC-MS 100 - 800 YMC	
Column	YMC ODS-A 120Å s - 5µ 50 mm x 3 mm id	
Gradient	5% - 90% acetonitrile in 0.05% trifluoroacetic acid linearly during 15 min at 1 mL/min	
Detection	UV: 214 nm	ELS: 40°C
MS	Experiment: Start:100 amu Stop: 800 amu Step: 0.2 amu Dwell: 0.571 msec Method Scan 284 times = 9.5 min State file* PPG-POS ddmmyy Cal file**Q1 MCAL ddmmyy	

*) The conditions for the ion source and ion analyser given in the state file are adjusted during the weekly tuning and maintenance of the instrument.

**) The mass calibration values given in the Calibration file is adjusted during the weekly tuning and maintenance of the instrument.

EXAMPLE 31:

N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(2-trifluoromethyl-phenyl)acetamide



Step 1: Coupling of aldehyde [building block 2] to resin[building block 1].

0.75 g resin (Wang resin loaded with 3-chloro-4-hydroxybenzoic acid hydrazide, [building block 1]) was swelled in dimethylformamide (6 mL) for 30 min and drained. The aldehyde (4-formyl-3-methoxyphenyl)carbamic acid 9H-fluoren-9-ylmethyl ester, 0.5 g, 1.36 mmol) dissolved in dimethylformamide (3 mL) was added followed by addition of triethylorthoformate (1.5 mL). The mixture was shaken for 16 hr at 20°C and drained. The resin was washed with dimethylformamide (5x4 mL), dichloromethane (5x4 mL) and dimethylformamide (5x4 mL). The coupling of the aldehyde was repeated twice.

Step 2: Deprotection of aniline.

The resin was swelled in dimethylformamide (5 mL) and piperidine added (1.25 mL). After shaking for 30 min, the resin was drained and washed with dimethylformamide (5x4 mL), N-methylpyrrolidinone (5x4 mL) and dimethylformamide (5x4 mL).

Step 3: Coupling of carboxylic acid [building block 3] to resin[building block 1][building block 2].

The resin[building block 1][building block 2] (0.5 g) was swelled in dimethylformamide (2.5 mL) and drained. The acid (2-trifluorophenylacetic acid, 2.3 mmol) was dissolved in dimethylformamide (2 mL) together with diisopropylcarbodiimide (2.3 mmol) and after 10 min this mixture was added to the drained resin. After 30 min of shaking a 1M solution of dimethylaminopyridine in dimethylformamide (0.32 mL) was added and the mixture was shaken for 16 hr and drained. The resin was washed with dimethylformamide (5x4 mL) and dichloromethane (5x4 mL). The coupling of the acid was repeated twice.

Step 4: Cleavage from the resin.

The resin was swelled in dichloromethane (2 mL) and trifluoroacetic acid (2 mL) was added. After shaking for 30 min the resin was drained. The eluent was collected and concentrated in vacuo. The residue was crystallized from methanol to the title compound.

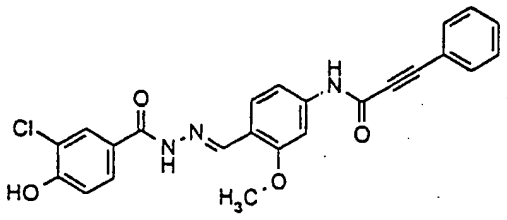
HPLC-MS (METHOD A) R_t = 6.5 min; m/z = 506.

^{1}H NMR, 400 MHz, (DMSO-d_6): δ 11.6 (s, 1H), 10.9 (s, 1H), 10.45 (s, 1H) 8.7 (s, 1H), 7.95 (s, 1H), 7.8-7.4 (m, 7H), 7.15 (d, 1H), 7.05 (d, 1H), 3.95 (s, 2H), 3.8 (s, 3H).

The following examples were prepared using the same synthesis methodology as described for the example above and can be prepared in parallel on solid support:

EXAMPLE 32:

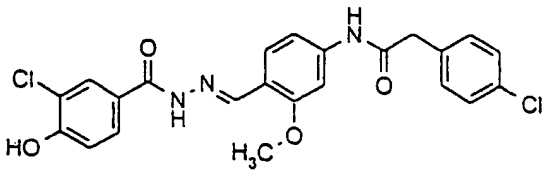
3-Phenylpropynoic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxy-phenyl}amide



HPLC-MS (METHOD A) R_t =5.95min; m/z = 448.

EXAMPLE 33:

N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-chlorophenyl)-acetamide

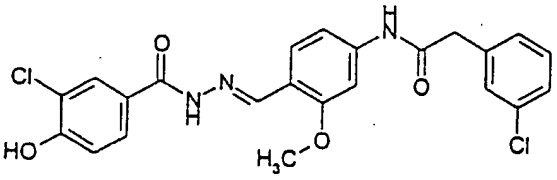


HPLC-MS (METHOD A) R_t = 6.33 min; m/z = 472.

^{1}H NMR, 400 MHz, (DMSO-d_6): δ 11.6 (s, 1H), 10.9 (s, 1H), 10.4 (s, 1H) 8.7 (s, 1H), 7.95 (s, 1H), 7.8-7.7 (m, 2H), 7.55 (s, 1H), 7.4-7.3 (m, 4H), 7.25 (d, 1H), 7.05 (d, 1H), 3.8 (s, 3H), 3.7 (s, 2H).

EXAMPLE 34:

N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3-chloro-phenyl)acetamide

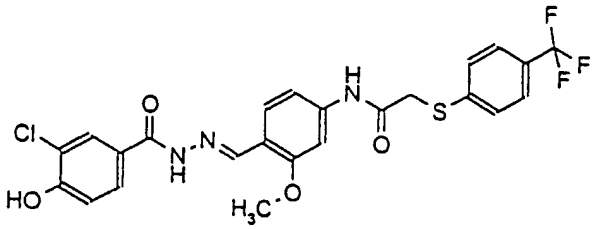


HPLC-MS (METHOD A) R_t = 6.33 min; m/z = 472.

^{1}H NMR, 400 MHz, (DMSO-d_6): δ 11.6 (s, 1H), 10.9 (s, 1H), 10.4 (s, 1H) 8.7 (s, 1H), 7.95 (s, 1H), 7.8-7.7 (m, 2H), 7.55 (s, 1H), 7.4-7.25 (m, 4H), 7.15 (d, 1H), 7.05 (d, 1H), 3.8 (s, 3H), 3.7 (s, 2H).

EXAMPLE 35:

N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-trifluoromethyl-phenylsulfanyl)acetamide

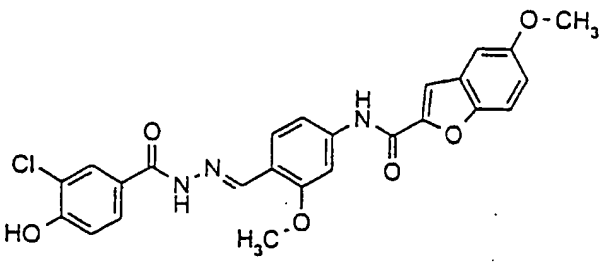


HPLC-MS (METHOD A) R_t = 6.88 min; m/z = 538.

^{1}H NMR, 400 MHz, (DMSO-d_6): δ 11.6 (s, 1H), 10.9 (s, 1H), 10.5 (s, 1H) 8.7 (s, 1H), 8.0 (s, 1H), 7.8-7.7 (m, 2H), 7.65 (d, 2H), 7.6 (d, 2H), 7.5 (s, 1H), 7.15 (d, 1H), 7.05 (d, 1H), 4.05 (s, 2H), 3.8 (s, 3H).

EXAMPLE 36:

5-Methoxybenzofuran-2-carboxylic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}amide



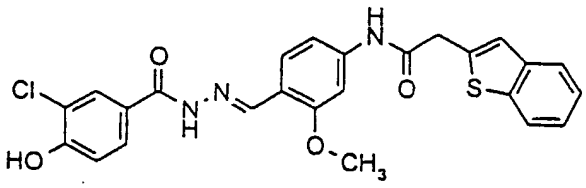
HPLC-MS (METHOD A) R_t = 6.42 min; m/z = 494.

Micro analysis: Calculated for $C_{25}H_{20}N_3O_6Cl$, 0.2 mole CH_2Cl_2: C, 58.87; H, 4.01; N, 8.16%. Found: C, 59.33; H, 4.31; N, 8.17%.

^{1}H NMR, 400 MHz, (DMSO-d_6): δ 11.7 (s, 1H), 10.9 (s, 1H), 10.6 (s, 1H) 8.7 (s, 1H), 8.0 (s, 1H), 7.9-7.7 (m, 4H), 7.6 (d, 1H), 7.55 (d, 1H), 7.3 (d, 1H), 7.1 (dd, 1H), 7.05 (d, 1H) 3.9 (s, 3H), 3.8 (s, 3H).

EXAMPLE 37:

2-Benzo[b]thiophen-3-yl-N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}acetamide



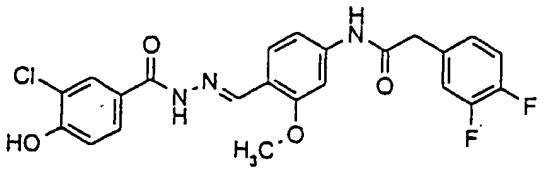
HPLC-MS (METHOD A) R_t = 6.1 min; m/z = 494.

Micro analysis: Calculated for $C_{25}H_{20}N_3O_4SCl$, $1\frac{1}{2}H_2O$: C, 57.64; H, 4.45; N, 8.07%. Found: C, 57.79; H, 3.96; N, 7.78%.

^{1}H NMR, 400 MHz, (DMSO-d_6): δ 11.6 (s, 1H), 10.9 (s, 1H), 10.5 (s, 1H) 8.7 (s, 1H), 8.1-7.7 (m, 4H), 7.6 (d, 2H), 7.45-7.35 (m, 3H), 7.2 (d, 1H), 7.05 (d, 1H), 3.95 (s, 2H), 3.8 (s, 3H).

EXAMPLE 38:

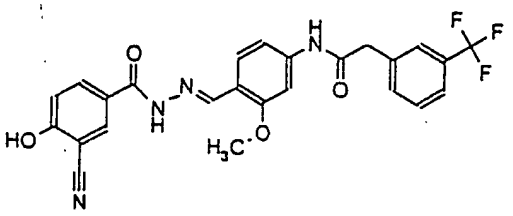
N-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3,4-difluorophenyl)acetamide



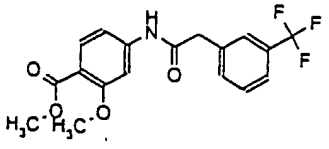
HPLC-MS (METHOD A) R_t = 6.12 min; m/z = 474.

^{1}H NMR, 400 MHz, (DMSO-d_6): δ 11.6 (s, 1H), 10.9 (s, 1H), 10.4 (s, 1H) 8.7 (s, 1H), 7.95 (s, 1H), 7.8-7.7 (m, 2H), 7.55 (s, 1H), 7.45-7.3 (m, 2H), 7.15 (d, 2H), 7.05 (d, 1H), 3.8 (s, 3H), 3.7 (s, 2H).

EXAMPLE 39: N-{4-[(3-Cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3-trifluoromethylphenyl)acetamide



2-Methoxy-4-[2-(3-trifluoromethylphenyl)acetylamino]benzoic acid methyl ester:



Diisopropylcarbodiimide (8.1 g, 42 mmol) was added to a solution of 3-(trifluoromethyl)-phenylacetic acid (17 g, 83 mmol) in dichloromethane (50 mL). After 10 min methyl 4-amino-2-methoxybenzoate (5.0 g, 28 mmol) was added and the mixture was stirred at reflux tem-

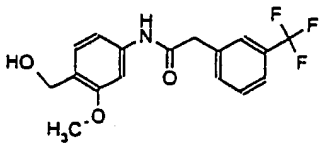
perature for 4 hr and at 20°C for 16 hr. The mixture was diluted with dichloromethane (100 mL) and extracted with a saturated solution of sodium hydrogen carbonate (3 x 50 mL) and water (3 x 50 mL). The organic phase was dried (magnesium sulphate), filtered and evaporated in vacuo to give crude 2-methoxy-4-[2-(3-trifluoromethylphenyl)acetetylamino]benzoic acid methyl ester that was purified by column chromatography on silica (120 g) using heptane and ethyl acetate (3:2) as eluent.

HPLC-MS (METHOD A) R_t = 6.17 min; m/z = 368.

Micro analysis: Calculated for $C_{18}H_{16}NO_4$: C, 58.86; H, 4.39; N, 3.81%
Found: C, 58.97; H, 4.41; N, 3.75%.

^{1}H NMR, 300 MHz, (DMSO-d_6): δ 10.5 (s, 1H), 7.7-7.5 (m, 6H), 7.2 (d, 1H), 3.85 (s, 2H), 3.75 (s, 3H), 3.7 (s, 3H).

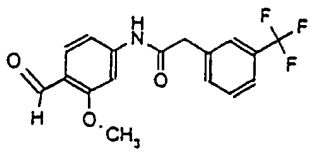
N-(4-Hydroxymethyl-3-methoxyphenyl)-2-(3-trifluoromethylphenyl)acetamide:



2-Methoxy-4-[2-(3-trifluoromethylphenyl)acetylamino]benzoic acid methyl ester (2.0 g, 5.4 mmol) was dissolved in dry dichloromethane (100 mL) under nitrogen and cooled to -20°C. Diisobutylaluminum hydride (1.2 M in toluene, 18.9 mmol, 16 mL) was dropwise added over 40min. The reaction mixture was heated to 20°C and stirred at this temperature for 2 hr. After dilution with dichloromethane (100 mL) the reaction mixture was quenched by dropwise addition of water (10 mL) at 20-25°C. The mixture was filtered after 16 hr and the organic phase was dried (magnesium sulphate), filtered and concentrated in vacuo to give crude N-(4-hydroxymethyl-3-methoxyphenyl)-2-(3-trifluoromethylphenyl)acetamide that was purified by column chromatography on silica (30 g) using heptane and ethyl acetate (3:2) as eluent.

^{1}H NMR, 300 MHz, (DMSO-d_6): δ 10.2 (s, 1H), 7.7-7.5 (m, 4H), 7.35 (s, 1H), 7.25 (d, 1H), 7.1 (d, 1H), 4.9 (t, 1H), 4.4 (d, 2H) 3.8 (s, 2H), 3.7 (s, 3H).

N-(4-Formyl-3-methoxyphenyl)-2-(3-trifluoromethylphenyl)acetamide:



N-(4-Hydroxymethyl-3-methoxyphenyl)-2-(3-trifluoromethylphenyl)acetamide (0.7 g, 2 mmol) was dissolved in ethyl acetate (40 mL) and manganese dioxide (3 g, 34 mmol) was added. The reaction mixture was stirred at 20°C for 3 hr and filtered. The organic phase was concentrated in vacuo to give crude N-(4-formyl-3-methoxyphenyl)-2-(3-trifluoromethylphenyl)-acetamide that was used for the next step without further purification.

^{1}H NMR, 300 MHz, (DMSO-d_6): δ 10.65 (s, 1H),10.2 (s, 1H), 7.7-7.5 (m, 6H), 7.2 (d, 1H), 3.85 (s, 5H).

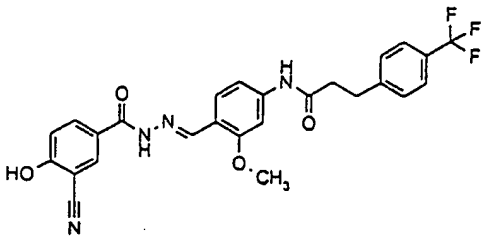
N-(4-Formyl-3-methoxyphenyl)-2-(3-trifluoromethylphenyl)acetamide (0.67 g, 2 mmol) was dissolved in dimethylsulfoxide (10 mL). 3-cyano-4-hydroxybenzoic acid hydrazide (0.35 g, 2 mmol) was added followed by addition of glacial acetic acid (0.3 mL). The reaction mixture was stirred for 16 hr at 20°C, diluted with ethyl acetate (125 mL) and washed with water (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL) and the organic phases combined, dried (magnesium sulphate) and concentrated in vacuo. The crude product was crystallised from methanol and dichloromethane (1:9) to give 0.5 g of the title compound.

HPLC-MS (METHOD A) R_t = 6.03 min; m/z = 497.

^{1}H NMR, 400 MHz, (DMSO-d_6): δ 11.8 (s, 1H), 11.7 (s, 1H), 10.5 (s, 1H), 8.7 (s, 1H), 8.2 (s, 1H), 8.05 (dd, 1H), 7.8 (d, 1H), 7.7 (s, 1H), 7.65-7.5 (m, 4H), 7.15 (d, 1H), 7.1 (d, 1H), 3.8 (s, 5H).

EXAMPLE 40:

N-{4-[(3-Cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-3-(4-trifluoromethyl-phenyl)propionamide



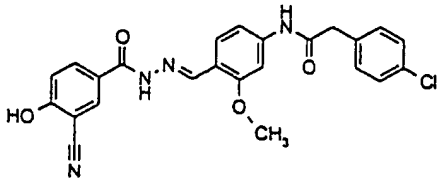
^{1}H NMR, 300 MHz, (DMSO-d_6): δ 11.8 (s, 1H), 11.7 (s, 1H), 10.2 (s, 1H), 8.68 (s, 1H), 8.24 (d, 1H), 8.06 (dd, 1H), 7.80 (d, 1H), 7.68 (d, 2H), 7.5 (m, 3H), 7.18 (d, 1H), 7.12 (d, 1H), 3.83 (s, 3H), 3.03 (t, 2H), 2.72 (t, 2H).

HPLC-MS (METHOD A) R_t = 5.62 min; m/z = 511.

Micro analysis: Calculated for $C_{26}H_{21}N_4O_4F_3$, ½ DMSO, 1 H_2O: C, 57.14; H, 4.62; N, 9.87%. Found: C, 57.18; H, 4.60; N, 9.78%.

EXAMPLE 41:

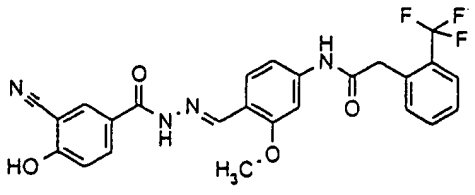
N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-chlorophenyl)-acetamide

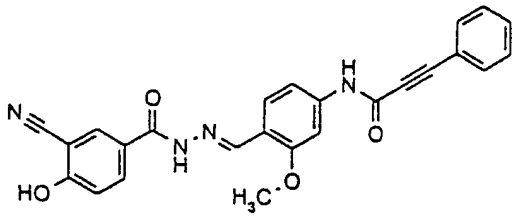


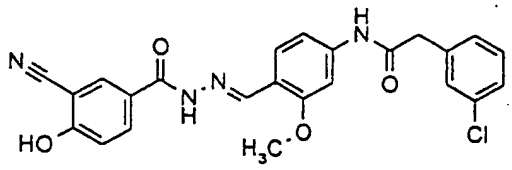
^{1}H NMR, 300 MHz, (DMSO-d_6): δ 11.8 (bs, 1H), 11.6 (s, 1H), 10.4 (s, 1H), 8.68 (s, 1H), 8.24 (d, 1H), 8.07 (dd, 1H), 7.80 (d, 1H), 7.55 (s, 1H), 7.4-7.35 (m, 5H), 7.18 (d, 1H), 7.10 (d, 2H), 3.82 (s, 3H), 3.68 (s, 2H).

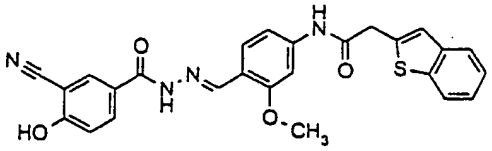
HPLC-MS (METHOD A) R_t = 5.33 min; m/z = 463.

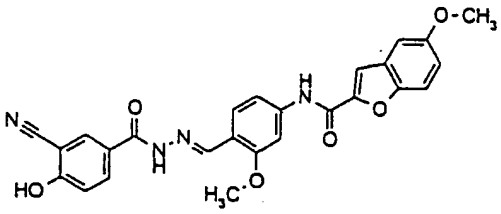
The following compounds may be prepared using the same synthesis methodology as described above:

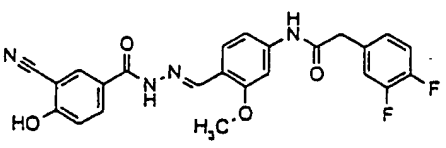


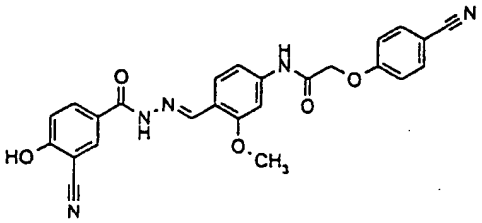


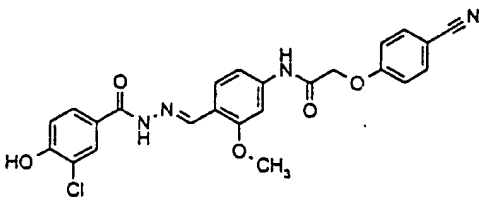


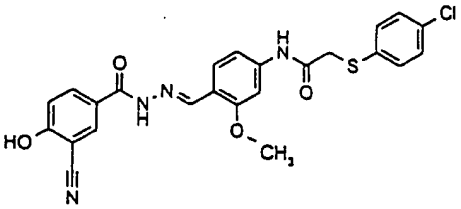


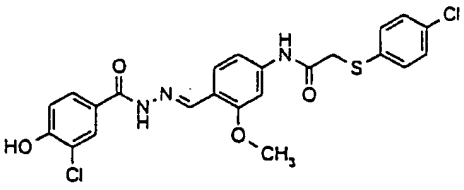


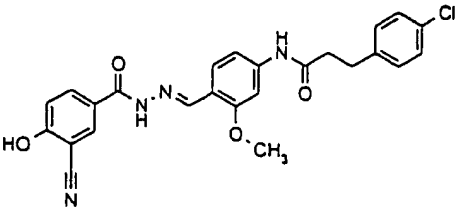


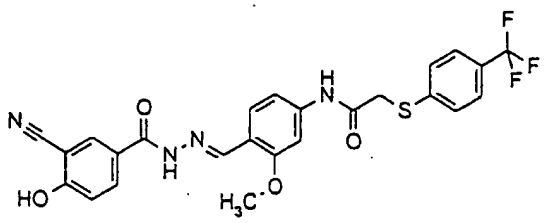




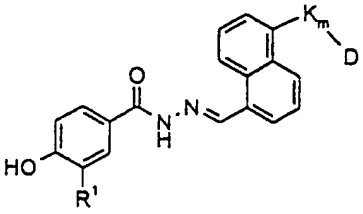








In yet a further aspect the invention relates to 1,5-substituted naphthalenes of the general formula (III):



(III)

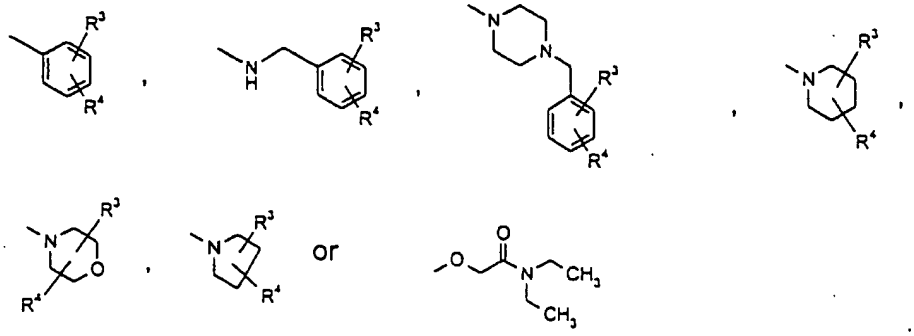
wherein

R^1 is chloro, fluoro, nitro or cyano;

K is

m is 0 or 1;

D is halogen, hydroxy,

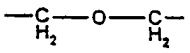
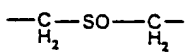
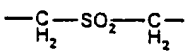


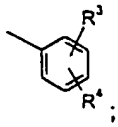
wherein

R^3 and R^4 independently are hydrogen, halogen, cyano, trifluoromethyl, trifluoromethoxy or C_{1-6}-alkyl;

with the proviso that

when K is

 ,  or  ;

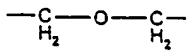
D is  ;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

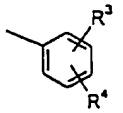
In a preferred embodiment R^1 is chloro.

More preferred R^1 is cyano.

In still a preferred embodiment m is 1, K is

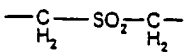


and D is

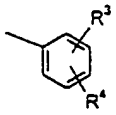


wherein R^3 and R^4 are as defined for formula (III) above.

In another preferred embodiment m is 1, K is

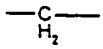


and D is

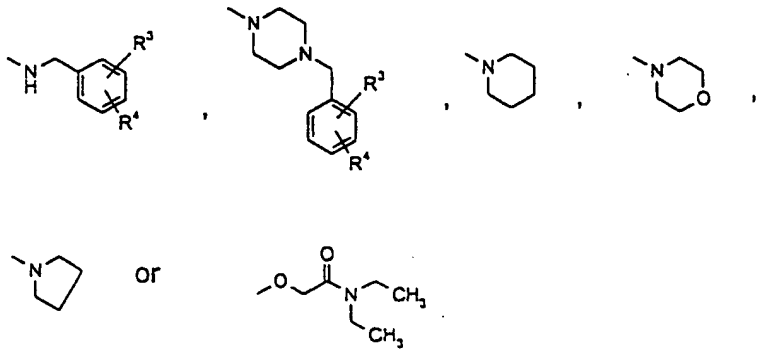


wherein R^3 and R^4 are as defined for formula (III) above.

In another preferred embodiment m is 1, K is



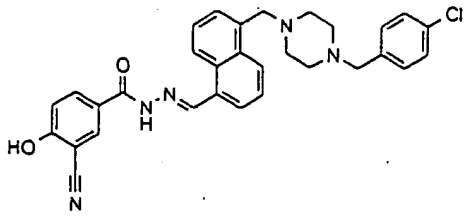
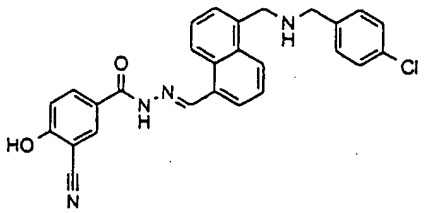
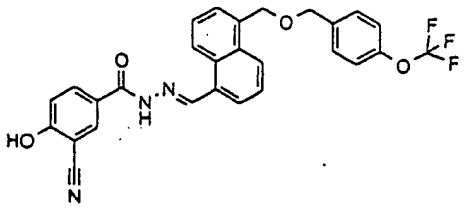
and D is halogen, hydroxy,



wherein R^3 and R^4 are as defined above for formula (III).

In the above preferred embodiments R^3 is preferably hydrogen and R^4 is halogen, cyano, trifluoromethyl, trifluoromethoxy or C_{1-6}-alkyl .

In a further preferred embodiment the invention relates to the following compounds:

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

The present invention is further illustrated by the following representative examples which are, however, not intended to limit the scope of the invention in any way.

Preparation of intermediates:

5-Hydroxymethyl-1-naphthaldehyde

Methyl 5-bromo-1-naphthylcarboxylate:

To a suspension of 5-bromo-1-naphthylcarboxylic acid (5 g, 20 mmol) in 200 mL anhydrous MeOH was added 5 mL concentrated H_2SO_4 and refluxed overnight. The reaction was cooled to room temperature and concentrated to one-third the volume. The residue was diluted with water and extracted with diethyl ether. The organic layer was separated and washed with water (2x), dried over $MgSO_4$, and concentrated. Silica gel column chromatography using hexane/ethyl acetate (2/1) gave 4.91 g (92%) of the product.

^{1}H NMR ($CDCl_3$): δ 4.01 (s, 3H), 7.44 (dd, 1H), 7.61 (dd, 1H), 7.85 (dd, 1H), 8.22 (dd, 1H), 8.51 (d, 1H), 8.90 (d, 1H).

Methyl 5-cyano-1-naphthylcarboxylate:

A mixture of methyl 5-bromo-1-naphthylcarboxylate (5.2 g, 19 mmol) and CuCN (3.4 g, 38 mmol) in 100 mL anhydrous dimethylformamide was refluxed overnight. After cooling the reaction to 70°C, a solution of NaCN (2 g) in 50 mL water was added to destroy the copper complex. Ethyl acetate was added and the two layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography using hexane/ethyl acetate (5/1) gave the product (3.8 g, 95%).

^1H NMR ($CDCl_3$): δ 4.01 (s, 3H), 7.60 - 7.80 (m, 3H), 7.98 (d, 1H), 8.30 (d, 1H), 8.45 (d, 1H), 9.21 (d, 1H).

5-Hydroxymethyl-1-naphthaldehyde:

To a cooled (0°C) solution of methyl 5-cyano-1-naphthylcarboxylate (1 g, 5 mmol) in 20 mL anhydrous tetrahydrofuran was added DIBAL (1M in hexane, 20 mL, 20 mmol) via syringe. The mixture was then kept between 50 - 60°C overnight. The mixture was then cooled to room temperature. The mixture was poured into a cold (0°C) solution of 2 N HCl (100 mL). The product was extracted with ether (2x). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. Silica gel column chromatography using hexane/ethyl acetate (2/1) gave 0.85 g (91%) of the product.

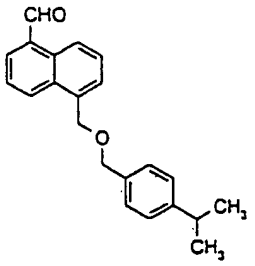
^1H NMR ($CDCl_3$): δ 4.95 (s, 2H), 7.45 - 7.58 (m, 3H), 7.82 (dd, 1H), 8.24 (d, 1H), 9.03 (dd, 1H), 10.21 (s, 1H).

General procedure for the alkylation of 5-hydroxymethyl-1-naphthaldehyde:

To a solution of the above 5-hydroxymethyl-1-naphthaldehyde (1 mmol), alkyl halide (1.5 mmol) and 100 mg n-Bu_4NCl in 20 mL CH_2Cl_2 was added aqueous 5% KOH (20 mL) solution. The reaction was refluxed overnight, and the two layers were separated. The organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated. The desired product was purified via silica gel column chromatography using hexane/ethyl acetate.

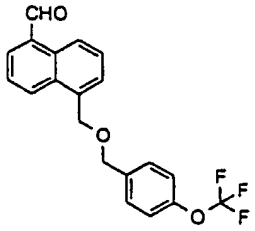
Examples of alkylated products:

5-(4-Isopropylbenzyloxy)methyl-1-naphthaldehyde:



^{1}H NMR ($CDCl_3$): δ 1.25 (d, 6H), 2.90 (m, 1H), 4.56 (s, 2H), 4.98 (s, 2H), 7.25 (dd, 4H), 7.52 - 7.68 (m, 3H), 7.97 (d, 1H), 8.42 (d, 1H), 9.24 (d, 1H), 10.38 (s, 1H).

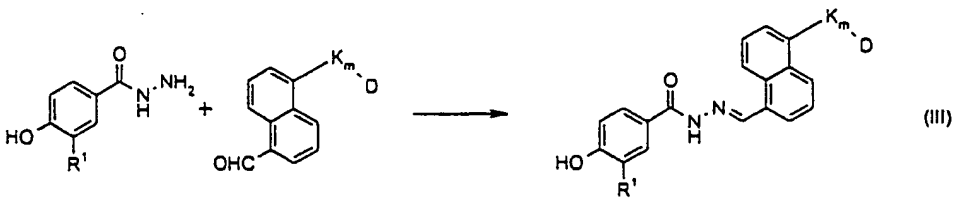
5-(4-Trifluoromethoxybenzyloxy)methyl-1-naphthaldehyde



^{1}H NMR ($CDCl_3$): δ 4.54 (s, 2H), 5.05 (s, 2H), 7.21(d, 2H), 7.39 (d, 2H), 7.59 - 7.74 (m, 3H), 8.01(d, 1H), 8.45 (d, 1H), 9.30 (d; 1H), 10.43 (s, 1H).

General procedure for the formation of the 1,5-substituted naphthalenes of the general formula (III):

SCHEME (III)



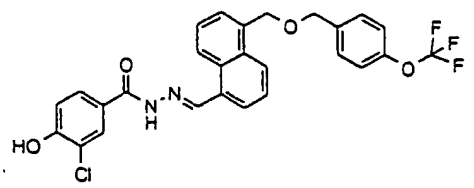
(III)

wherein R^1, K, m and D are as defined for formula (III) above.

The resulting carbonyl compounds, prepared as described above, are treated with the corresponding acylhydrazide prepared as decribed in the foregoing in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, dimethylsulfoxide, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of N_2 or Ar at temperatures between 0°C to 140°C, preferably between 10°C to 80°C. In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate.

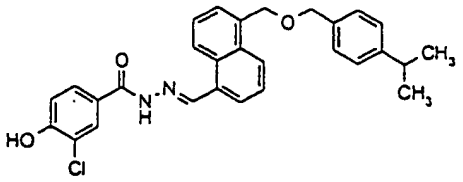
The following compounds of the general formula (III) according to the invention were prepared as examples of compounds that can be prepared using this methodology:

EXAMPLE 42:



^{1}H NMR (DMSO-d_6): δ 4.67 (s, 2H), 5.05 (s, 2H), 7.11 (d, 1H), 7.35 (d, 2H), 7.50 (d, 2H), 7.57 - 7.75 (m, 3H), 7.82 (d, 1H), 7.95 - 8.08 (m, 2H), 8.22 (d, 1H), 8.78 (s, 1H), 9.14 (s, 1H), 11.01 (s, 1H), 11.85 (s, 1H); LC-MS (APCI, neg.): 527.

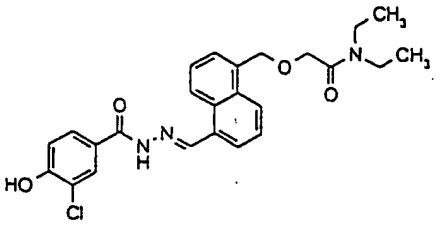
EXAMPLE 43:



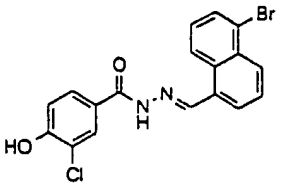
^{1}H NMR (DMSO-d_6): δ 1.13 (d, 6H), 2.82 (m, 1H), 4.53 (s, 2H), 4.95 (d, 2H), 7.04 (d, 1H), 7.15 - 7.24 (dd, 4H), 7.57 - 7.62 (m, 3H), 7.76 (d, 1H), 7.90 - 7.97 (m, 2H), 8.14 (d, 1H), 8.70 (s, 1H), 9.08 (s, 1H), 10.99 (s, 1H), 11.78 (s, 1H).

LC-MS (APCI, neg.): 485.1.

EXAMPLE 44:

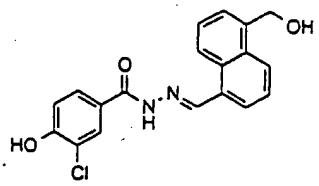


EXAMPLE 45:



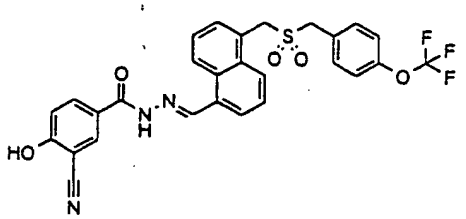
^{1}H NMR (DMSO-d_6): δ 7.09 (d, 1H), 7.58 (t, 1H), 7.79 (m, 2H), 7.96 - 8.01 (m, 3H), 8.27 (d, 1H), 8.86 (d, 1H), 9.09 (s, 1H), 11.0 (s, 1H), 11.88 (s, 1H); LC-MS (APCI, neg.): 403.1.

EXAMPLE 46:



^{1}H NMR (DMSO-d_6) δ 4.98 (d, 2H), 5.37 (t, 1H), 7.08 (d, 1H), 7.62 (dr, 3H), 7.79 (d, 1H), 7.94 (d, 1H), 8.00 (s, 1H), 8.18 (d, 1H), 8.67 (s, 1H), 9.12 (s, 1H); LC-MS (APCI, pos.): 355.

EXAMPLE 47:

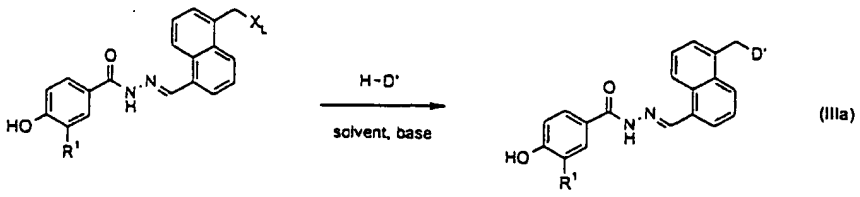


^{1}H NMR (DMSO-d_6): δ 11.8 (b, 1H), 10.5 (b, 1H), 9.0 (s, 1H), 8.7 (d, 1H), 8.1 (m, 2H), 8.0 (d, 1H), 7.9 (d, 1H), 7.5 (m, 6H), 7.3 (d, 2H), 7.0 (d, 2H), 5.0 (s, 1H), 4.6 (s, 1H);
MS (M+1): 568.

<u>General procedure for the synthesis of further derivatized hydrazides of the general formula (IIIa):</u>

According to one embodiment of the invention the compounds of the general formula (IIIa) may be prepared as indicated in the below Scheme (IIIa), that is, by converting an alkylidene hydrazide (prepared according to the general method shown above) into a further derivatized alkylidene hydrazide. Thus, by reacting an amine with an alkylidene hydrazide that contains a leaving group X_L such as Cl, Br or OSO_2Me, a new alkylidene hydrazide of formula (IIIa) can be formed.

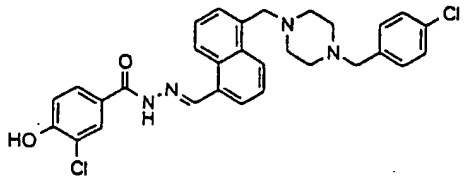
SCHEME (IIIa)



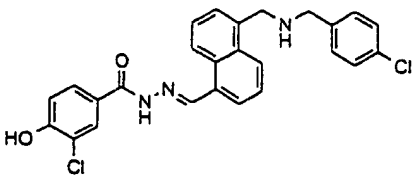
wherein X_L is a leaving group, such as chloro, bromo or OSO_2CH_3, R^1 is as defined for formula (III) and D' is the subset of D that contains a primary or secondary amine that can react as a nucleophile.

Specific examples illustrating the preparation of further derivatized hydrazides of formula (III) are provided below:

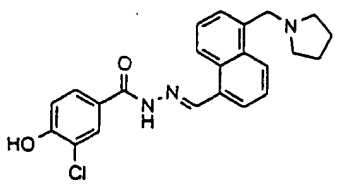
EXAMPLE 48:



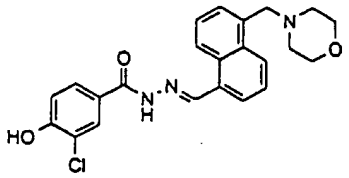
EXAMPLE 49:



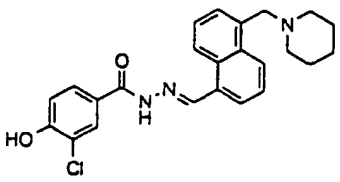
EXAMPLE 50:



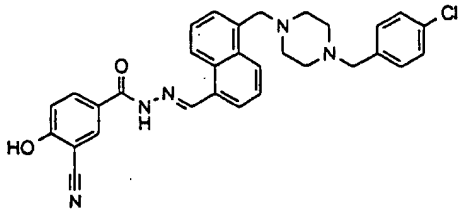
EXAMPLE 51:

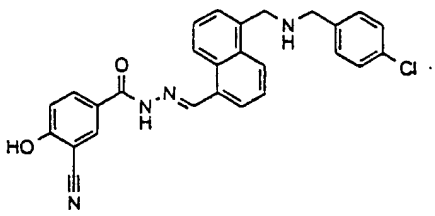


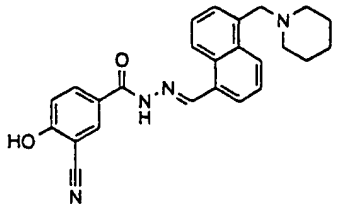
EXAMPLE 52:

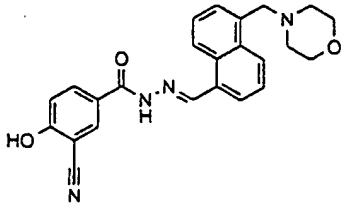


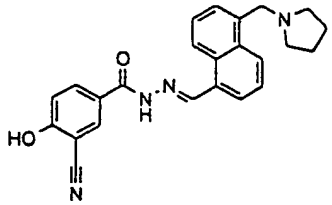
The following compounds of the formula (III) may also be prepared using the above mentioned methodologies:

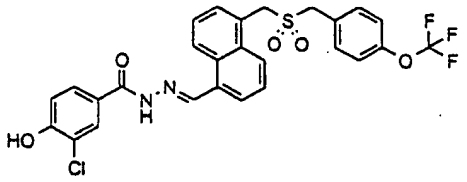


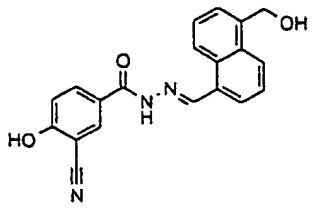


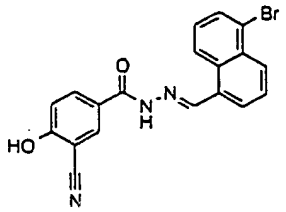


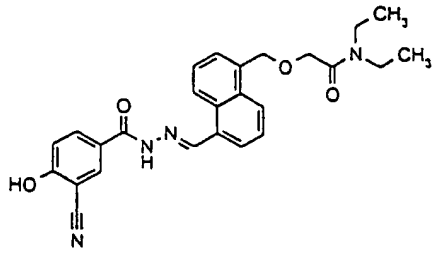


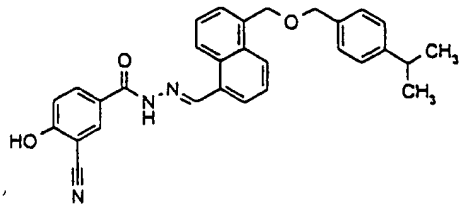


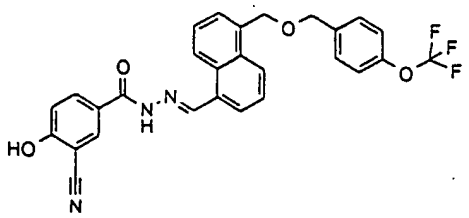




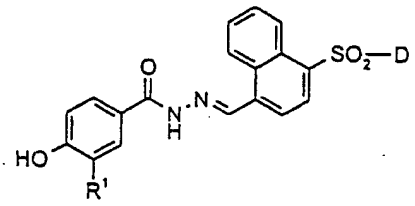








In yet a further aspect the invention relates to the naphthalene sulfonamides of the general formula (IV):

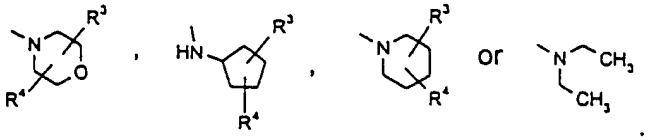


(IV)

wherein

R^1 is chloro, fluoro, nitro or cyano;

D is



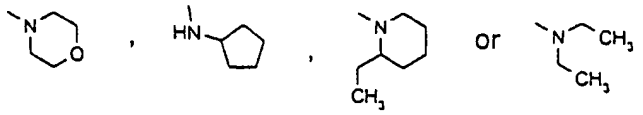
;

wherein

R^3 and R^4 independently are hydrogen, halogen, cyano, trifluoromethyl, trifluoromethoxy or C_{1-6}-alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the invention D is



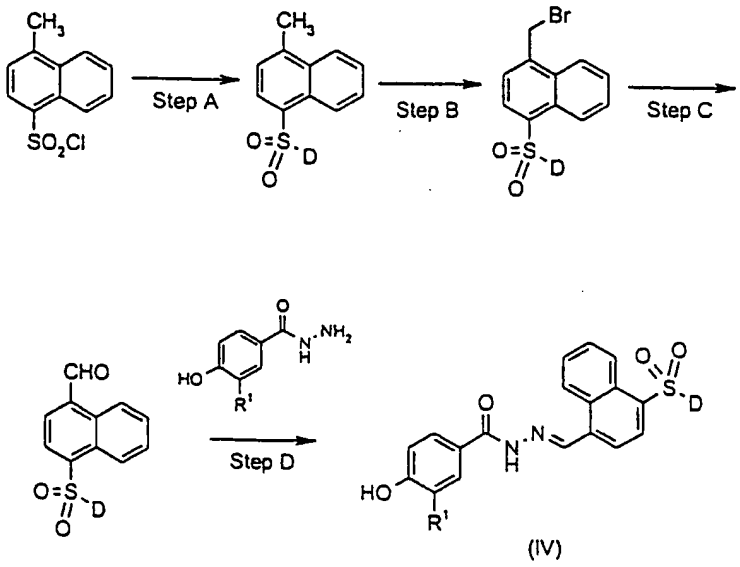
In another preferred embodiment of the invention R^1 is chloro.

More preferred R^1 is cyano.

The present invention is further illustrated by the following representative examples which are, however, not intended to limit the scope of the invention in any way.

General procedure for the preparation of hydrazones of naphthalene sulfonamides of the formula (IV):

SCHEME (IV)



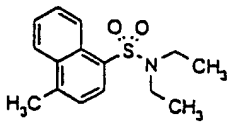
Step A: General procedure for the synthesis of 4-methyl-1-naphthalene sulfonamides.

To a solution of 4-methyl-1-naphthalene sulfonylchloride (2.0 g, 8.3 mmol) (prepared according to P. Cagniant, D. Cagniant, Bull.Soc. Chim. Fr. 1966, 2037-2042) in dichloromethane was added dropwise the amine (1eq) at 0°C. The mixture was stirred at room tem-

perature for 16 hr, diluted with dichloromethane (15 mL), extracted with 1N HCl (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated to give the corresponding 4-methyl-1-naphthalene sulfonamide.

Examples of sulfonamides prepared:

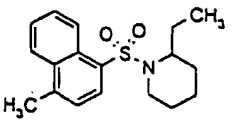
4-Methyl-1-naphthalene diethylsulfonamide:



^1H NMR ($CDCl_3$): δ 1.08 (t, J = 6.8 Hz, 6H), 2.76 (s, 3H), 3.37 (q, J = 6.8 Hz, 4H), 7.37 (d, J = 7.5 Hz, 1H), 7.61 – 7.66 (m, 2H), 8.08 (dd, J = 2.1, 4.2 Hz, 1H), 8.11 (d, J = 7.5 Hz, 1H), 8.67 (dd, J = 2.1, 8.6 Hz, 1H).

GC-MS (pos.): 278.

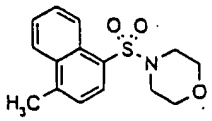
1-(2-Ethylpiperidinylsulfonyl)-4-methylnaphthalene:



^1H NMR ($CDCl_3$): δ 0.74 (t, J = 6.8 Hz, 3H), 1.21 (m, 2H), 1.47–1.66 (m, 6H), 2.76 (s, 3H), 3.01 (t, J = 13.4 Hz, 1H), 3.69 (dd, J = 3.5, 13.4 Hz, 1H), 3.99 (m, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.61–7.66 (m, 2H), 8.08 (dd, J = 2.1, 6.5 Hz, 1H), 8.20 (d, J = 7.5 Hz, 1H), 8.62 (dd, J = 2.1, 9.5 Hz, 1H).

GC-MS (pos.): 318.

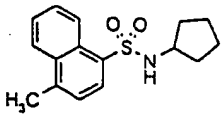
1-(4-Morpholinosulfonyl)-4-methylnaphthalene:



^{1}H NMR ($CDCl_3$): δ 2.78 (s, 3H), 3.15 (t, J = 4.7 Hz, 4H), 3.68 (t, J = 4.7 Hz, 4H), 7.42 (d, J = 7.5 Hz, 1H), 7.63 – 7.67 (m, 2H), 8.09 – 8.14 (m, 2H), 8.78 – 8.81 (m, 1H).

GC-MS (pos.): 292.

4-Methyl-1-naphthalene cyclopentylsulfonamide:



^{1}H NMR ($CDCl_3$): δ 1.21 – 1.66 (m, 8H), 2.78 (s, 3H), 3.54 (m, 1H), 4.60 (d, J = 7.3 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.63 – 7.68 (m, 2H), 8.12 (dd, J = 2.0, 7.6 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H), 8.65 (dd, J = 1.8, 7.2 Hz, 1H); GC-MS (pos.): 290.

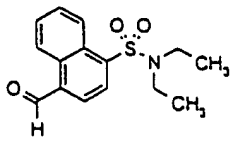
Step B: General procedure for the synthesis of 4-bromomethyl-1-naphthalene sulfonamides. A mixture of 4-methyl-1-naphthalene sulfonamide (1 eq), N-bromosuccinimide (1.1 eq) and a catalytic amount of benzoyl peroxide in CCl_4 was refluxed for 2 hr. The mixture was filtered, and the filtrate was concentrated. Flash chromatography (hexane:ethyl acetate, 5:1) provided a mixture of starting material and desired product, which was used without further purification in the next step.

Step C: General procedure for the synthesis of 4-formyl-1-naphthalene sulfonamides. Nitrogen was bubbled through a suspension of 1.3 g sodium bicarbonate in dimethylsulfoxide (5 mL) for 20 min. The 4-bromomethyl-1-naphthalene sulfonamide from step B dissolved in 5 mL dimethylsulfoxide was added. The mixture was placed in oil bath at 110°C for 1.5 hr. The mixture was cooled, diluted with water (10 mL), and extracted with ethyl acetate (3x10

mL). The combined organic extracts were dried ($MgSO_4$), and concentrated. Flash chromatography (silicagel, hexane:ethyl acetate, 5:1) provided the title compound.

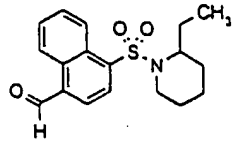
Examples of 4-formyl-1-naphthalene sulfonamides:

4-Formyl-1-naphthalene diethylsulfonamide:



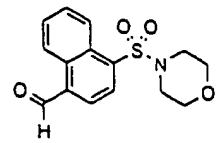
^{1}H NMR ($CDCl_3$): δ 1.12 (t, J = 6.8 Hz, 6H), 3.41 (q, J = 6.8 Hz, 4H), 7.74 – 7.79 (m, 2H), 8.04 (d, J = 7.5 Hz, 1H), 8.32 (d, J =7.5 Hz, 1H), 8.78 (dd, J = 2.1, 7.7 Hz, 1H), 9.28 (dd, J = 2.1, 6.7 Hz, 1H), 10.50 (s, 1H). GC-MS (pos.): 292.

1-(2-Ethylpiperidinylsulfonyl)-4-formylnaphthalene:



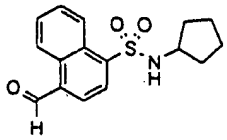
^{1}H NMR ($CDCl_3$): δ 0.74 (t, J = 6.8 Hz, 3H), 1.21 (m, 2H), 1.47–1.66 (m, 6H), 3.02 (dd, J = 2.2, 11.2 Hz, 1H), 3.72 (dd, J = 3.6 Hz, 1H), 3.97 (m, 1 H), 7.73–7.78 (m, 2H), 8.04 (d, J = 7.6 Hz, 1H), 8.45 (d, J = 7.5 Hz, 1H), 8.73 (dd, J = 2.1, 7.8 Hz, 1 H), 9.28 (dd, J = 2.1, 6.7 Hz, 1H), 10.50 (s, 1H).

1-(4-Morpholinosulfonyl)-4-formylnaphthalene:



^{1}H NMR ($CDCl_3$): δ 3.21 (t, J = 4.7 Hz, 4H), 3.70 (t, J = 4.7 Hz, 4H), 7.73–7.78 (m, 2H), 8.08 (d, J = 7.6 Hz, 1H), 8.37 (d, J = 7.5 Hz, 1H), 8.87 (d, J = 7.5 Hz, 1H), 9.30 (dd, J = 8.0 Hz, 1H), 10.52 (s, 1H).

4-Formyl-1-naphthalene cyclopentylsulfonamide:

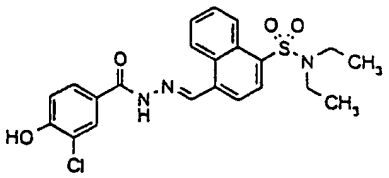


^{1}H NMR ($CDCl_3$): δ 1.23–1.27 (m, 2H), 1.42–1.53 (m, 4H), 1.62–1.69 (m, 2H), 3.65 (m, 1H), 4.82 (d, J = 7.5 Hz, 1H), 7.73–7.82 (m, 2H), 8.07 (d, J = 7.6 Hz, 1H), 8.46 (d, J = 7.5 Hz, 1H), 8.75 (dd, J = 2.2, 7.6 Hz, 1H), 9.31 (dd, J =2.2, 6.7 Hz, 1H), 10.51 (s, 1H).

Step D: General procedure for the synthesis of the naphthalene sulfonamides of the general formula (IV).

These compounds were prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 4-formyl-1-naphthalene sulfonamides from step C and the appropriate 3-substituted 4-hydroxy benzoic acid hydrazide.

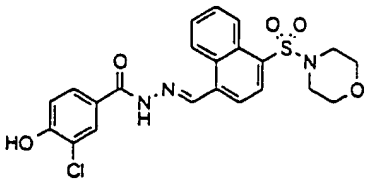
EXAMPLE 53: 4-{[2-(3-Chloro-4-hydroxybenzoyl)hydrazono]methyl}-N,N-diethyl-1-naphthalenesulfonamide



^{1}H NMR (DMSO-d_6): δ 1.11 (t, J = 7.0 Hz, 6H), 3.32 (q, J = 7.0 Hz, 4H), 7.09 (d, J = 8.5 Hz, 1H), 7.79 (m, 3H), 8.01–8.17 (m, 3H), 8.63 (m, 1 H), 7.79 (m, 1H), 9.16 (s, 1 H), 11.20 (bs, 1H), 12.02 (s, 1H); MS (APCI, pos.): 460.1, 462.1.

EXAMPLE 54:

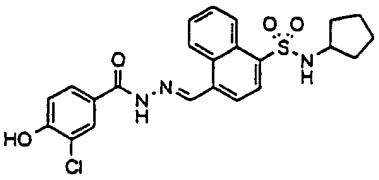
3-Chloro-4-hydroxybenzoyl)-N-4[-(4-morpholinosulfonyl)-1-naphthyl]-methylene hydrazide



^{1}H NMR (DMSO-d_6): δ 3.08 (m, 4H), 3.74 (m, 4H), 7.09 (d, J = 8.3 Hz, 1H), 7.78-7.83 (m, 4H), 8.00 (s, 1H), 8.13 (m, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.72–8.76 (m, 2 H), 9.17 (s, 1H), 12.06 (s, 1H); MS (APCI, pos.): 474.0, 476.1.

EXAMPLE 55:

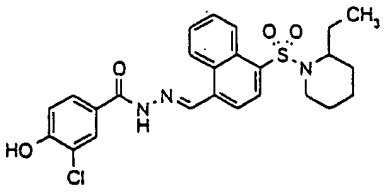
4-{[2-(3-Chloro-4-hydroxybenzoyl)hydrazono]methyl}-N-cyclopentyl-1-naphthalenesulfonamide



^{1}H NMR (DMSO-d_6): δ 1.15 – 1.25 (m, 4H), 1.27 (m, 4H), 3.40 (m, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.75 – 7.80 (m, 3H), 7.98 (s, 1 H), 8.04 – 8.07 (m, 2H), 8.22 (d, J = 7.8 Hz, 1H), 8.73 – 8.77 (m, 2H), 9.15 (s, 1H), 12.00 (s, 1H); MS (APCI, pos.): 472, 474.

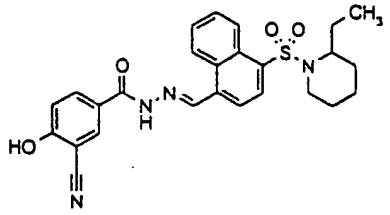
EXAMPLE 56:

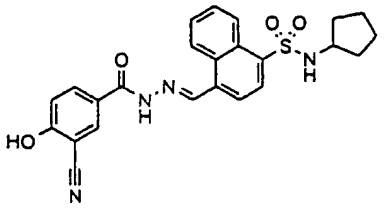
3-Chloro-4-hydroxybenzoic acid 4-[(2-ethyl-1-piperidinyl)sulfonyl]-1-naphthylmethylene hydrazide

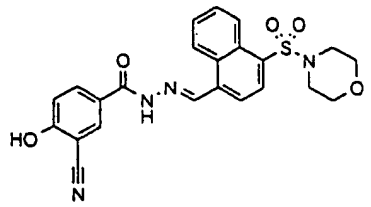


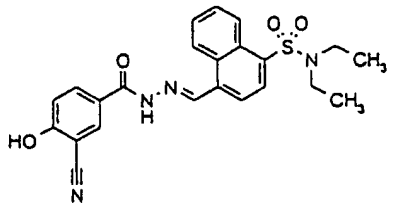
^{1}H NMR (DMSO-d_6): δ 0.64 (t, J = 6.8 Hz, 3H), 0.93 (m, 2H), 1.22–1.66 (m, 6H), 3.02 (t, J = 11.2 Hz, 1H), 3.72 (m, 1H), 3.85 (m, 1 H), 7.08 (d, J = 8.5 Hz, 1 H), 7.75 – 7.80 (m, 3H), 8.01 (s, 1H), 8.07 (d, J = 8.7 Hz, 1 H), 8.30 (d, J = 7.8 Hz, 1H), 8.62 (m, 1H), 8.76 (m, 1 H), 9.17 (s, 1H), 12.00 (s, 1H); MS (APCI, pos.): 500, 502.

The following compounds of the formula (IV) may also be prepared using the above mentioned methodologies:

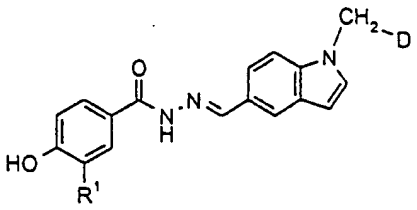








In another aspect the invention relates to 1,5-alkylated indoles of the formula (V):

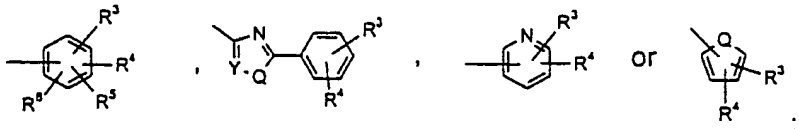


(V)

wherein

R^1 is chloro, fluoro, nitro or cyano;

D is



;

wherein

Q is -O- or -S-;

Y is -CH= or -N=;

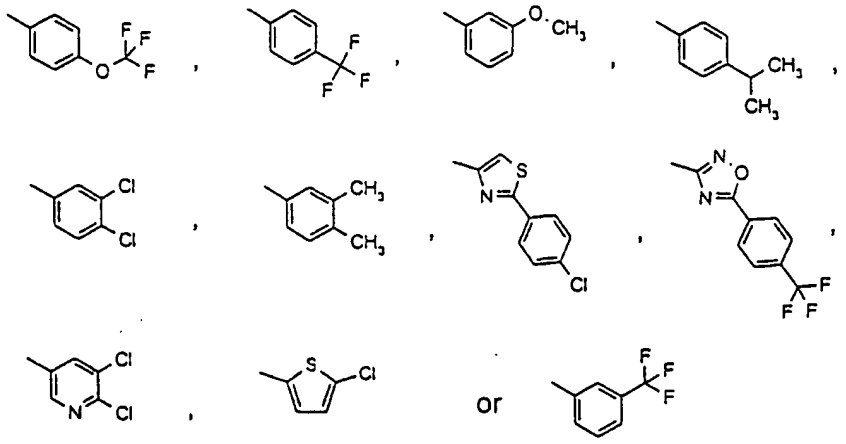
R^3, R^4, R^5 and R^6 independently are hydrogen, C_{1-6}-alkyl, trifluoromethyl, trifluoromethoxy, halogen or C_{1-6}-alkoxy;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a preferred embodiment R^1 is chloro.

More preferred R^1 is cyano.

In still another preferred embodiment D is

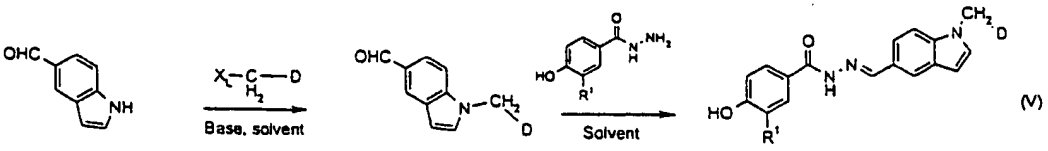


The present invention is further illustrated by the following representative examples which are, however, not intended to limit the scope of the invention in any way.

General procedure for the synthesis of 1-substituted indole-5-carboxaldehydes followed by hydrazone formation:

The 1-substituted indole-5-carboxaldehydes may be prepared according to the below Scheme (V) by N-alkylation of the indole-4-carboxaldehyde using various electrophilic alkylating agents that introduce the $-CH_2-D$ moiety as defined above such as halides (fluorides, chlorides, bromides, iodides), methanesulfonates, toluenesulfonates or triflates.

SCHEME (V)



wherein X_L is a leaving group such as -F, -Cl, -Br, -I, $-OSO_2CH_3$, $-OSO_2$p-tolyl or $-OSO_2CF_3$ and D and R^1 are as defined for formula (V).

According to Scheme (V) 1-substituted indole-5-carboxaldehydes can be prepared by stirring indole-5-carboxaldehyde in an organic solvent such as acetone, methylethyl ketone, dimethylformamide, dioxane, tetrahydrofuran, toluene, ethylene glycol dimethyl ether, sulfolane, dieth-

ylether, dimethylsulfoxide, water or a compatible mixture of two or more of the above solvents with an equimolar amount of the appropriate halide in the presence of 1 to 15 equivalents (preferably 1 to 5 equivalents) of a base such as sodium hydride, potassium hydride, sodium or potassium methoxide, ethoxide or *tert*-butoxide, sodium, potassium or cesium carbonate, potassium or cesium fluoride, sodium or potassium hydroxide or organic bases such as diisopropylethylamine, 2,4,6-collidine or benzyldimethyl- ammonium methoxide or hydroxide. The reaction can be performed at 0°C to 150°C, preferably at 20°C to 100°C and preferably in an inert atmosphere of N_2 or Ar. When the reaction is complete the mixture is filtered, concentrated in vacuo and the resulting product optionally purified by column chromatography on silica gel using ethyl acetate/hexane as eluent. The compound can also (when appropriate) be purified by recrystallization from a suitable solvent such as ethyl alcohol, ethyl acetate, isopropyl alcohol, water, hexane, toluene or their compatible mixture.

The resulting carbonyl compounds are then treated with the corresponding acylhydrazide in a solvent. The solvent may be one of the following: ethyl alcohol, methyl alcohol, isopropyl alcohol, *tert*-butyl alcohol, dioxane, tetrahydrofuran, toluene, chlorobenzene, anisole, benzene, chloroform, dichloromethane, dimethylsulfoxide, acetic acid, water or a compatible mixture of two or more of the above solvents. A catalyst such as acetic acid or trifluoroacetic acid can be added. A dehydrating reagent such as triethylorthoformate can also be added to the reaction mixture. The reaction is performed by stirring the reaction mixture preferably under an inert atmosphere of N_2 or Ar at temperatures between 0°C to 140°C, preferably between 10°C to 80°C. In many cases the product simply crystallizes out when the reaction is completed and is isolated by suction filtration. It can be further recrystallized if necessary from a solvent such as the above described reaction solvents. The product can also be isolated by concentration of the reaction mixture in vacuo, followed by column chromatography on silica gel using a solvent system such as chloroform/methanol or dichloromethane/methanol or chloroform/ethyl acetate.

Library procedure for indole alkylation:

Preparation of the sodium salt of the indole:

Indole-5-carboxaldehyde (1.45 g) was dissolved into 8.6 mL of dry dimethylformamide in a dried and cooled 100 mL 3-necked round bottom flask. While maintaining a steady flow of nitrogen or argon through the 3-necked round bottomed flask, 1.1 equivalent of sodium hy-

dride (0.27 g of dry 95% reagent) was transferred to the indole solution. The mixture was stirred for 15 minutes, while maintaining flow of inert gas.

Preparation of the halide solutions:

Amber glass vials (for preparing stock solutions) were dried for at least four hours at 110 °C, then were allowed to cool under an argon atmosphere in a desiccator. Halide solutions (1.0 M) were prepared in anhydrous dimethylformamide in the dried vials. Each halide solution (100 µL) was added to its corresponding well of a deep-well plate.

Alkylation of the indole sodium salt:

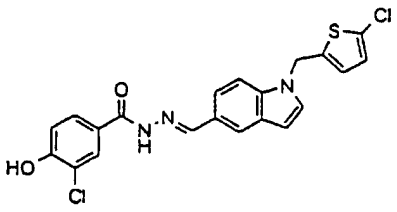
100 µL of the 1.0 M indole salt solution was quickly delivered to each alkyl halide in the deep-well plates. The plates were vortexed briefly to mix, then allowed to react for two hours.

Library procedure for hydrazone formation:

3-Substituted 4-hydroxybenzoic acid hydrazides (10 mmoles) were dissolved in 5 mL of dry dimethylsulfoxide, followed by trifluoroacetic acid (0.77 mL). The resulting solutions were diluted to final volumes of 10.0 mL. 100 µL of the 1.0 M acid hydrazide trifluoroacetic acid salt solution was added to each well of the deep-well plate. The plate was vortexed for one minute to mix, then allowed to react for 30 minutes.

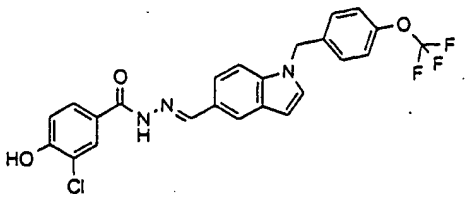
The products were purified by chromatography on silica gel with ethyl acetate/hexane eluent.

EXAMPLE 57:



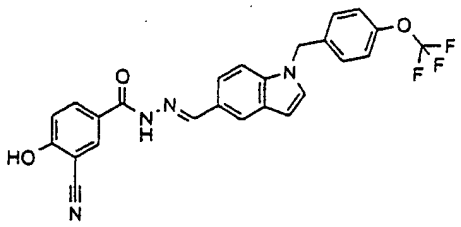
^{1}H NMR (DMSO-d_6): δ 5.54 (s, 2H), 7.07 (d, 1H), 7.20 (t, 1H), 7.26 (m, 2H), 7.31 (s, 4H), 7.58 (d, 1H), 7.68 (s, 1H), 7.80 (d, 1H), 8.01 (d, 1H), 8.66 (s, 1H), 11.98 (brd s, 1H), 11.71 (s, 1H); MS (APCI, negative): 486.0, 487.0, 488.0.

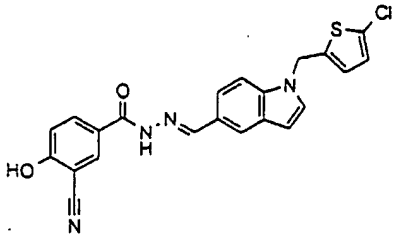
EXAMPLE 58:

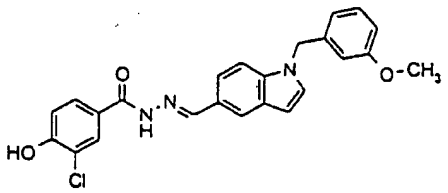


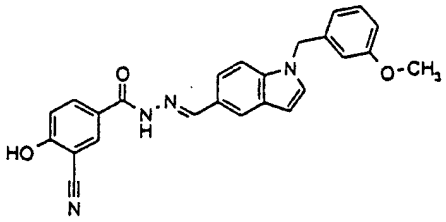
^{1}H NMR (DMSO-d_6): δ 5.54 (s, 2H), 7.08 (d, 1H), 7.19 (t, 1H), 7.27-7.31 (m, 5H), 7.57 (d, 1H), 7.67 (s, 1H), 7.80 (d, 1H), 8.01 (d, 1H), 8.66 (s, 1H), 10.97 (brd s, 1H), 11.71 (s, 1H); MS (APCI, neg.): 486.0, 487.0, 488.0.

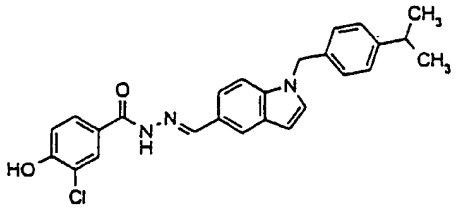
Similarly, the following compounds of the formula (V) may be prepared:

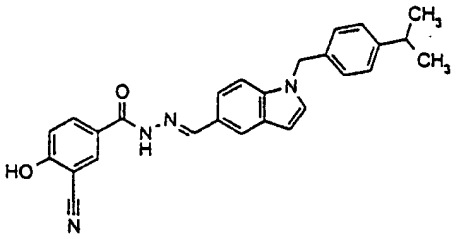


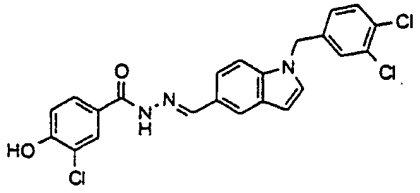


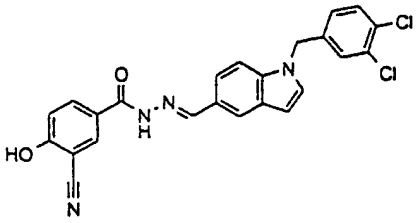


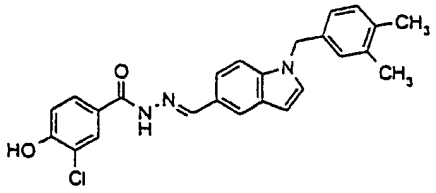


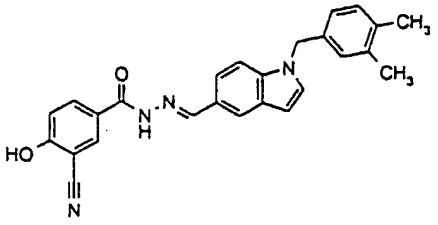


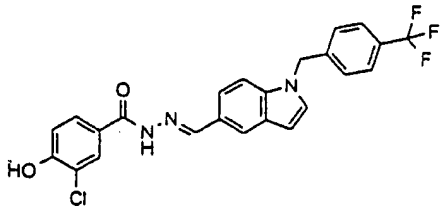


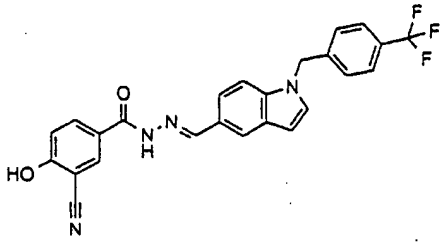


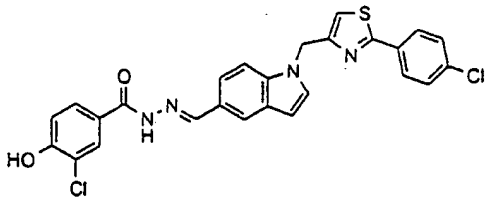


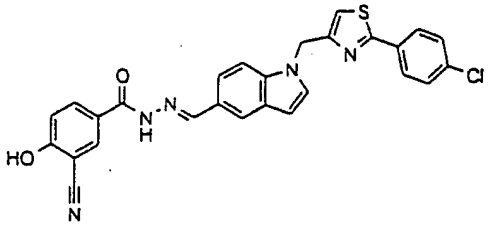


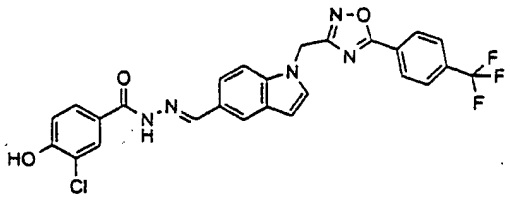


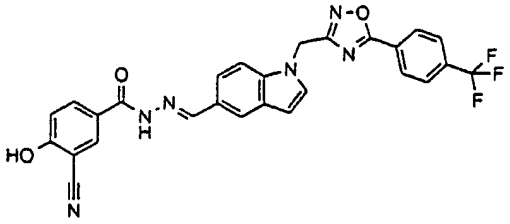


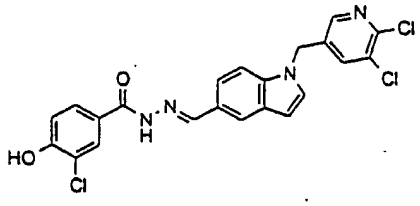


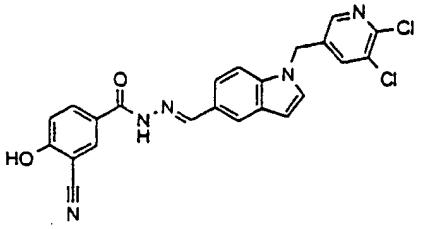


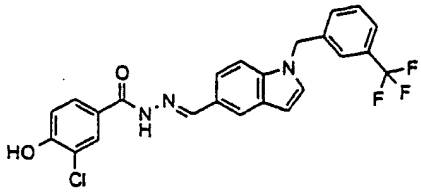


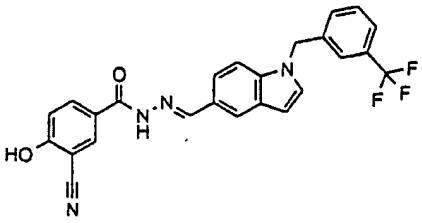




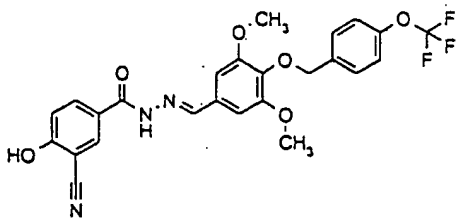




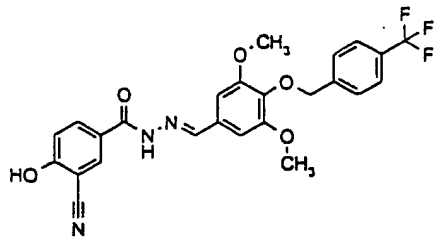




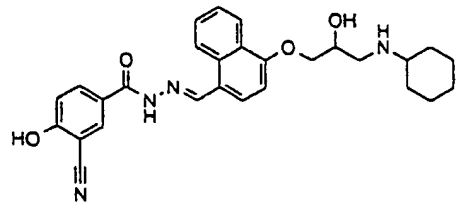
In a further aspect the invention relates to the following compounds:



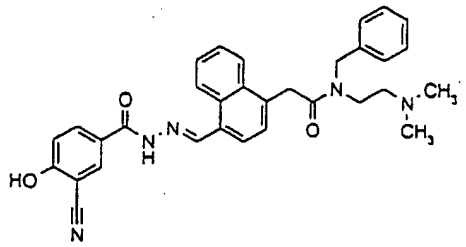
^{1}H NMR (DMSO-d_6): δ 3.83 (s, 6H), 4.98 (s, 2H), 7.03 (s, 2H) 7.14 (d, 1H), 7.36 (d, 2H), 7.58 (d, 2H), 8.04 (d, 1H), 8.21 (s, 1H), 8.35 (s, 1H), 11.80 (bs, 2H); MS (APCI, pos.): 517.2;



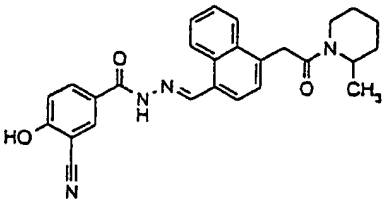
^{1}H NMR (DMSO-d_6): δ 3,83 (s, 6H), 5.05 (s, 2H), 7.03 (s, 2H), 7.12 (d, 1H), 7.69 (d, 2H), 7.74 (d, 2H), 8.03 (dd, 1H), 8.20 (d, 1H), 8.34 (s, 1H), 11.80 (s, 1H), 11.89 (s, 1H); MS (APCI, pos.): 500.1;



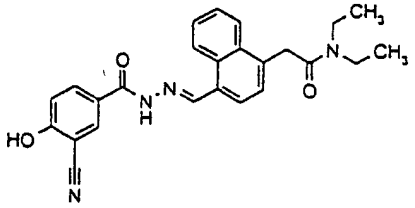
^{1}H NMR (DMSO-d_6): δ 1.00-2.00 (m, 10H), 2.76 (m, 1H), 2.97 (m, 1H), 3.09 (m, 1H), 4.20 (s, 3H), 6.58 (d, 1H), 7.07 (d, 1H), 7.53-7.70 (m, 2H), 7.78-7.81 (d, 2H), 8.02 (s, 1H) 8.35 (d, 1H), 8.90-8.97 (d, 2H), 11.47 (s, 1H); LC-MS (APCI, pos.): 487;



^{1}H NMR (DMSO-d_6): δ 2.37 (s, 3H), 2.53 (s, 3H), 2.75-2.92 (d, 2H), 3.58-3.61 (d, 2H), 4.22 (s, 1H), 4.38 (s, 1H), 4.58 (s, 1H), 4.82 (s, 1H), 7.12 (d, 1H), 7.21-7.75 (m, 10H), 7.84 (d, 1H), 8.10 (t, 1H), 8.26 (s, 1H), 8.82 (t, 1H), 9.11 (s, 1H), 11.91 (s, 1H); LC-MS (APCI, pos.): 534;

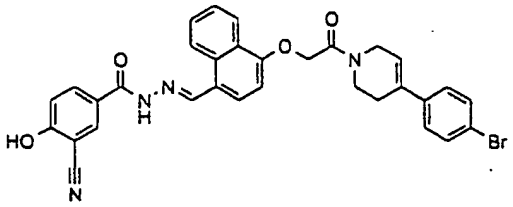


^{1}H NMR (DMSO-d_6): δ 1.08-1.32 (m, 4H), 1.50-1.59 (m, 5H), 2.66 (m, 0.5H), 3.12 (m, 0.5H), 3.77 (m, 0.5H), 4.17 (s, 2H), 4.27-4.32 (m, 1H), 4.74 (m, 0.5H), 7.14 (d, 1H), 7.43 (m, 1H), 7.64 (m, 2H), 7.87 (d, 1H), 8.01 (d, 1H), 8.10 (d, 1H), 8.27 (s, 1H), 8.85 (d, 1H), 9.05 (s, 1H), 11.86 (s, 2H); IR (KBr): 2230, 1608 cm^{-1}; MS (APCI, pos.): 455;

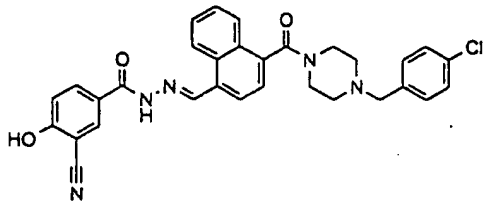


^{1}H NMR (DMSO-d_6): δ 1.04 (t, 3H), 1.15 (t, 3H), 3.29 (q, 2H), 3.45 (q, 2H), 4.18 (s, 2H), 7.15

(d, 1H), 3.45 (q, 2H), 4.18 (s, 2H), 7.15 (d, 1H), 7.43 (d, 1H), 7.57-7.68 (m, 2H), 7.87 (d, 1H), 8.09 (dd, 1H), 8.26 (s, 1H), 8.84 (d, 1H), 9.05 (s, 1H), 11.87 (bs, 2H); IR (KBr): 2229, 1607 cm^{-1}; MS (APCI, pos.): 429.2;



^{1}H NMR (DMSO-d_6): δ 2.54 (m, 1H), 2.61 (m, 1H), 3.74 (m, 2H), 4.15 (m, 1H), 4.28 (m, 1H), 5.19 (m, 1H), 5.24 (m, 1H), 6.26 (s, 1H), 7.07 (t, 1H), 7.16 (d, 1H), 7.41 (dd, 2H), 7.55 (d, 2H), 7.63 (dd, 1H), 7.71 (dd, 1H), 7.81 (d, 1H), 8.09 (d, 1H), 8.26 (s, 1H), 8.36 (d, 1H), 8.92 (s, 1H), 9.01 (d, 1H), 11.74 (s, 1H), 11.88 (s, 1H); MS (APCI, pos.): 610.0, 612.0;

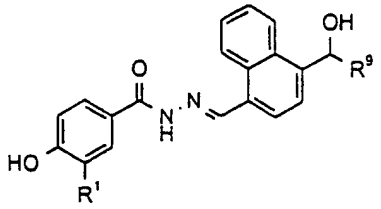


^{1}H NMR (DMSO-d_6): δ 2.21 (m, 1H), 2.29 (m, 1H), 2.50 (m, 2H), 3.11 (m, 2H), 3.49 (s, 2H), 3.84 (m, 1H), 3.88 (m, 1H), 7.16 (d, 1H), 7.31 (d, 2H), 7.37 (d, 2H), 7.52 (d, 1H), 7.66 (m, 2H), 7.83 (d, 1H), 7.96 (d, 1H), 8.11 (d, 1H), 8.28 (s, 1H), 8.87 (d, 1H), 9.08 (s, 1H), 11.95 (s, 1H); MS (APCI, pos.): 552.2;

as well as any optical or geometric isomers or tautomeric forms thereof including mixtures of these or a pharmaceutically acceptable salts thereof.

The compounds were prepared in analogy with the foregoing methods of preparation.

In another aspect the invention relates to the compounds of the general formula (VI):



(VI)

wherein

R^1 is chloro, fluoro, nitro or cyano;

R^9 is C_{1-6}-alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a preferred embodiment R^1 is chloro.

More preferred R^1 is cyano.

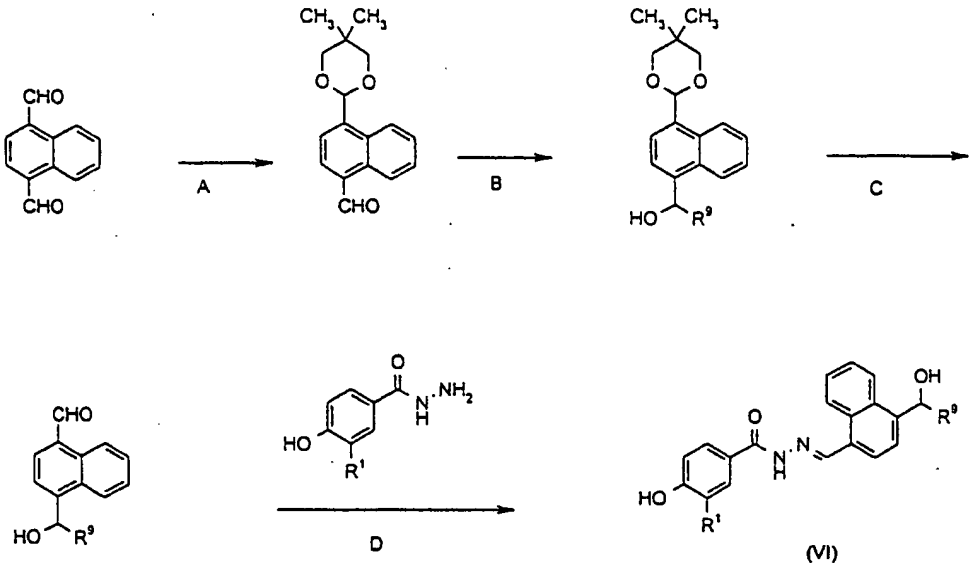
In another preferred embodiment the invention relates to 3-cyano-4-hydroxybenzoic acid [4-(1-hydroxy-3-methylbutyl)-naphth-1-ylmethylene] hydrazide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In yet another preferred embodiment the invention relates to 3-cyano-4-hydroxy-benzoic acid [4-(1-hydroxy-2-methylpropyl)-naphth-1-ylmethylene] hydrazide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

The present invention is further illustrated by the following representative examples of the formula (VI) which are, however, not intended to limit the scope of the invention in any way.

General procedure for the preparation of compounds according to formula (VI):

SCHEME (VI)



Step A: General procedure for the preparation of mono-protected naphthalene-1,4-dicarboxaldehydes.

To a solution of naphthalene-1,4-dicarboxaldehyde in a solvent, such as tetrahydrofuran, dichloromethane, toluene, benzene, or ethylenglycol dimethyl ether, is added a slight excess (1.1 equivalent) of a diol, such as 1,2-ethanediol, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol (neopentylglycol) and the like and an acidic catalyst, such as p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, BF_3-etherate. The resulting mixture is stirred at 20-150 °C, preferably at room temperature or at the boiling point of the mixture. Extraction and/or flash chromatography affords the desired mono-protected naphthalene-1,4-dicarboxaldehyde.

Step B: General procedure for the preparation of protected 4-(1-hydroxyalkyl)-naphthalene-1-carboxaldehydes.

To a solution of the mono-protected naphthalene-1,4-dicarboxaldehyde in tetrahydrofuran is added the desired alkyl magnesium chloride dissolved in tetrahydrofuran. The mixture is stirred at room temperature for 3 hr, diluted with satd. NH_4Cl, and extracted with ethyl ace-

tate. The combined organic extracts are dried ($MgSO_4$) and concentrated. The product is isolated by flash chromatography.

Step C: General procedure for the preparation of 4-(1-hydroxyalkyl)-naphthalene-1-carboxaldehydes.

Hydrolysis of the protected aldehyde is performed under acidic aqueous conditions, eg with a mixture of water and one of the following acids: hydrochloric acid, hydrobromic acid, trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid, perchloric acid or sulfuric acid. Extraction and flash chromatography affords the desired 4-(1-hydroxyalkyl)-naphthalene-1-carboxaldehyde.

In certain cases the protection/deprotection sequence (Step A and Step C) in the preparation of the 4-(1-hydroxyalkyl)-naphthalene-1-carboxaldehyde can be omitted as described below:

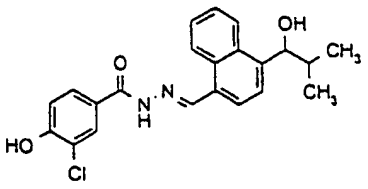
To a solution of 1,4-diformylnaphthalene in tetrahydrofuran is added the desired alkyl magnesium chloride dissolved in tetrahydrofuran. The mixture is stirred at room temperature for 3 hr, diluted with satd. NH_4Cl, and extracted with ethyl acetate. The combined organic extracts are dried ($MgSO_4$) and concentrated. The product is isolated by flash chromatography.

Step D: General procedure for the preparation of hydrazones.

Hydrazones are prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of the appropriate 3-substituted 4-hydroxybenzoic acid hydrazide and the above 4-(1-hydroxyalkyl)naphthaldehydes.

EXAMPLE 59:

3-Chloro-4-hydroxybenzoic acid [4-(1-hydroxy-2-methylpropyl)naphth-1-ylmethylene] hydrazide



4-Formyl-1-(1-hydroxy-2-methylpropyl) naphthalene:

To a solution of 1,4-diformylnaphthalene (490 mg, 2.66 mmol) in tetrahydrofuran (12 mL) was added dropwise at 0°C isopropyl magnesium chloride (1.3 mL of a 2 M solution in tetrahydrofuran). The mixture was stirred at room temperature for 3 hr, diluted with satd. NH_4Cl (10 mL), and extracted with ethyl acetate (3 x10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (silicagel, hexane:ethyl acetate, 5:1) provided the title compound (81 mg, 14%).

^1H NMR ($CDCl_3$): δ 0.83 (d, J = 6.5 Hz, 3H), 1.03 (d, J = 6.5 Hz, 3H), 2.24 (m, 1H), 5.21 (m, 1H), 5.33 (d, J = 4.5 Hz, 1H), 7.62 – 7.64 (m, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 7.4 Hz, 1H), 8.01 (d, J = 7.4 Hz, 1H), 8.15 (d, J = 7.8 Hz, 1H), 9.35 (d, J = 7.8 Hz, 1H), 10.29 (s, 1H); GC-MS: 228.

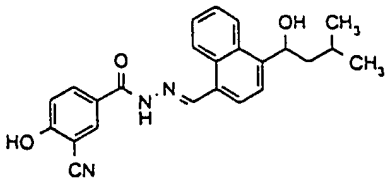
3-Chloro-4-hydroxybenzoic acid 4-(1-hydroxy-2-methylpropyl)naphthyl methylene hydrazide:

The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 4-formyl-1-(1-hydroxy-2-methylpropyl) naphthalene and 3-chloro-4-hydroxy benzoic acid hydrazide.

^1H NMR (DMSO-d_6): δ 0.88 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H), 2.03 (m, 1H), 5.11 (dd, J = J'= 4.5 Hz, 1H), 5.38 (d, J = 4.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.62 (m, 2H), 7.69 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H), 8.00 (d, J = 1.8 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.82 (d, J = 8.0 Hz, 1H), 9.07 (s, 1H), 11.04 (s, 1H), 11.78 (s, 1H); MS (APCI, pos.): 397.1, 399.1.

EXAMPLE 60:

3-Cyano-4-hydroxybenzoic acid [4-(1-hydroxy-3-methylbutyl)-naphth-1-ylmethylene] hydrazide



Step A: 4-(5,5-Dimethyl-1,3-dioxan-2-yl)-1-naphthaldehyde.

A solution of 1,4-diformylnaphthalene (4.1 g, 22 mmol) [prep. acc. Ried et al. Chem. Ber. 91, 1958, 2479] neopentylglycole (2.1 g, 24 mmol), and p-TsOH (250 mg) in toluene (100 mL) was refluxed for 16 hours using a Dean-Stark-trap to remove water. The solution was extracted with satd. $NaHCO_3$ solution (3 x 30 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silicagel, hexane:ethyl acetate, 9:1) to provide 4.0 g (66%) of the desired product.

^1H NMR ($CDCl_3$): δ 0.88 (s, 3H), 1.37 (s, 3H), 3.80 (d, J = 11.0 Hz, 2H), 3.91 (d, J =11.0 Hz, 2H), 6.04 (s, 1H), 7.09 (m, 2H), 7.45 (m, 2H), 7.65 (d, J = 7.7 Hz, 1H), 8.75 (d, J=7.7 Hz, 1H), 9.83 (s, 1H); GC-MS (pos.): 270.

Step B: 1-[4-(5,5-Dimethyl-1,3-dioxan-2-yl)-1-naphthyl]-3-methyl-1-butanol.

4-(5,5-Dimethyl-1,3-dioxan-2-yl)-1-naphthaldehyde (4.0 g, 14.8 mmol) was dissolved in diethyl ether (80 mL).Magnesium bromide diethyl etherate (2.8 g, 10.8 mol) was added followed by a 2M solution of isobutyl magnesium chloride in diethyl ether (8.0 mL, 16 mmol). The mixture was stirred at room temperature for 16 hours, diluted with methanol (1 mL), water (1 mL), and 1 N HCl (20 mL). The phases were separated, and the aqueous phase was extracted with ether (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated. Flash chromatography of the residue provided the 1.76 g (36%) desired product.

^1H NMR ($CDCl_3$): δ 0.87 (s, 3H), 0.97 (d, J = 6.7 Hz, 3H), 1.14 (d, J = 6.7 Hz, 3H), 1.67-2.11 (m, 4H), 5.65 (d, J = 8.0 Hz, 1H), 5.98 (s, 1 H), 7.60-7.72 (m, 2H), 7.90 (d, J = 7.5 Hz, 1H), 8.00 (d, J = 7.5 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 9.34 (d, J = 8.2 Hz, 1H), 10.36 (s, 1H); GC-MS (pos.): 243.

Step C: 4-(1-Hydroxy-3-methylbutyl)-1-naphthaldehyde.

To a solution of 1-[4-(5,5-dimethyl-1,3-dioxan-2-yl)-1-naphthyl]-3-methyl-1-butanol (1.76 g, 5.35 mmol) in tetrahydrofuran (10 mL) was added water (1mL) and conc. HCl (1mL). The solution was stirred at room temp. for 16 hr, diluted with $NaHCO_3$-solution (20 mL), and extracted with ether (3 x 30 mL). The combined organic extracts were dried and concentrated. Flash chromatography (silicagel, hexanes:ethyl acetate, 4:1) provided 900 mg (70%) colourless oil.

^1H NMR ($CDCl_3$): δ 0.99 (d, J = 6.7 Hz, 3H), 1.08 (d, J = 6.7 Hz, 3H), 1.36 (s, 3H), 1.67-1.92 (m, 4H), 5.55 (d, J = 8.9 Hz, 1H), 5.98 (s, 1 H), 7.57 (m, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 8.11 (dd, J = 2.5, 7.2 Hz, 1H), 8.24 (dd, J = 2.5, 8.5 Hz, 1H).

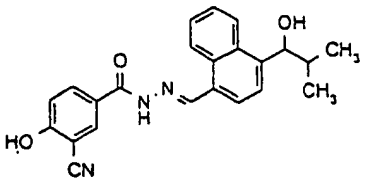
Step D: 3-Cyano-4-hydroxybenzoic acid 4-(1-hydroxy-3-methylbutyl)naphthyl methylidene hydrazide.

The compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of 4-(1-hydroxy-3-methylbutyl)-1-naphthaldehyde from step C and 3-cyano-4-hydroxy benzoic acid hydrazide.

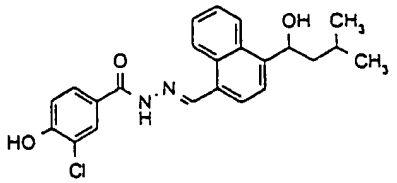
^1H NMR (DMSO-d_6): δ 0.89 (d, J = 6.6 Hz, 3 H), 1.05 (d, j = 6.6 Hz, 3 H), 1.50 (m, 1H), 1.61 (m, 1H), 1.63 (m, 1H), 5.39 (m, 2H), 7.15 (d, J = 8.8 Hz, 1H), 7.64 (m, 2H), 7.76 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 8.27 (s, 1H), 8.85 (d, J = 7.8 Hz, 1H), 9.05 (s, 1 H), 11.84 (s, 1H), 11.89 (s, 1H); MS (APCI, pos.): 402.

By use of the aforementioned methodology the following compounds may be produced:

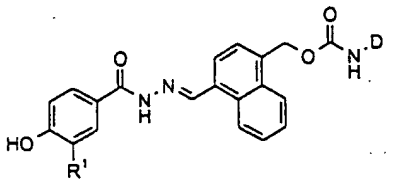
3-Cyano-4-hydroxy-benzoic acid [4-(1-hydroxy-2-methylpropyl)-naphth-1-yl-methylene] hydrazide



3-Chloro-4-hydroxy-benzoic acid [4-(1-hydroxy-3-methylbutyl)-naphth-1-yl-methylene] hydrazide



In another aspect the invention relates to the compounds of the general formula (VII):

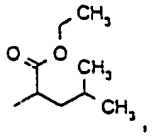


(VII)

wherein

R^1 is nitro, fluoro, chloro or cyano;

D is C_{1-6}-alkyl,

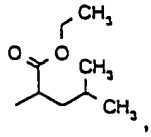
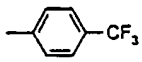
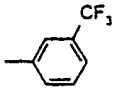
 ,  or  ;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a preferred embodiment R^1 is chloro.

More preferred R^1 is cyano.

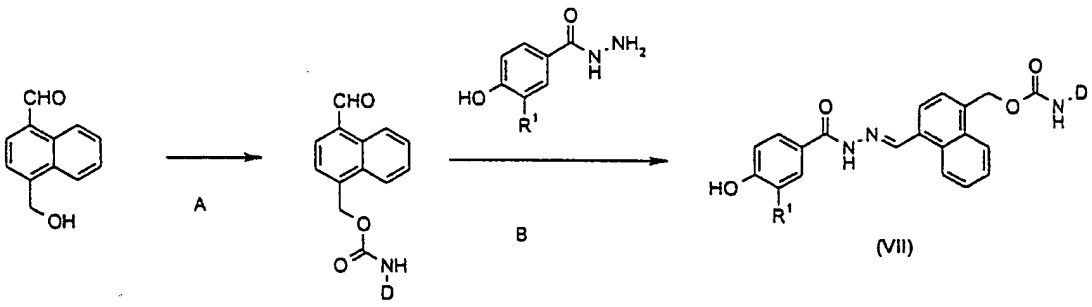
In another preferred embodiment D is isopropyl,

 ,  ,  or  .

The present invention is further illustrated by the following representative examples which are, however, not intended to limit the scope of the invention in any way.

General procedure for the preparation of compounds described by the general formula (VII):

SCHEME (VII)



(VII)

Step A: General procedure for the preparation of carbamates.

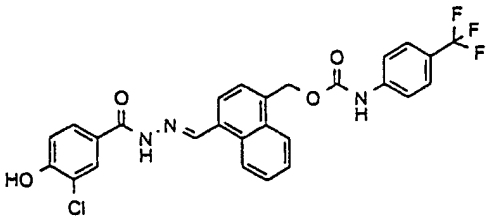
To a solution of hydroxymethylnaphthaldehyde dissolved in anhydrous dimethylformamide is added the desired isocyanate (excess). After stirring the reaction overnight at room temperature, hexane was added to help precipitate the product. The crude product was collected by filtration and recrystallized from dichloromethane.

Step B: General procedure for the preparation of hydrazones.

Hydrazones were prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of the appropriate 3-substituted 4-hydroxybenzoic acid hydrazide and the above carbamate-aldehydes.

EXAMPLE 61:

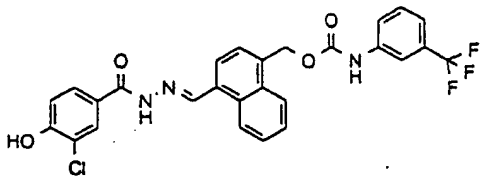
(4-Trifluoromethylphenyl)carbamic acid 4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-naphth-1-ylmethyl ester



^{1}H NMR (DMSO-d_6): δ 5.70 (s, 2H), 7.09 (d, 1H), 7.66 (m, 4H), 7.73 (m, 3H), 7.80 (d, 1H), 7.94 (d, 1H), 8.00 (d, 1H), 8.20 (m, 1H), 8.90 (d, 1H), 9.10 (d, 1H), 10.24 (s, 1H), 10.99 (brd s, 1H) 11.85 (brd s, 1H); MS (APCI): 541.8, 543.8.

EXAMPLE 62:

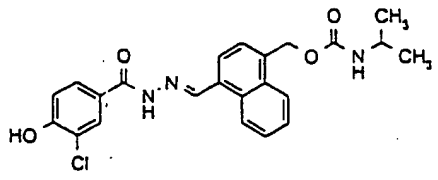
(3-Trifluoromethylphenyl)carbamic acid 4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-naphth-1-ylmethyl ester



^{1}H NMR (DMSO-d_6): δ 5.69 (s, 2H), 7.12 (d, 1H), 7.33 (d, 1H), 7.51 (t, 3H), 7.68 - 7.75 (m, 2H), 7.84 (d, 1H), 7.93 (s, 1H), 7.96 (d, 1H), 8.04 (s, 1H), 8.20 (m, 1H), 8.86 (d, 1H), 9.22 (s, 1H) 10.20 (s, 1H) 11.10 (brd s, 1H), 12.01 (brd s, 1H); MS (APCI): 541.8, 543.8.

EXAMPLE 63:

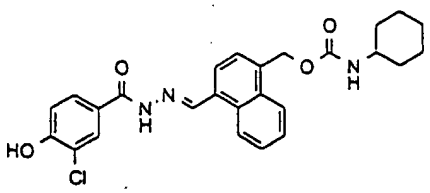
Isopropylcarbamic acid 4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-ylmethylester



^{1}H NMR (DMSO-d_6): δ 1.06 (d, 6H), 3.62 (oct, 1H), 5.51 (s, 2H), 7.08 (d, 1H), 7.22 (d, 1H), 7.62 - 7.69 (m, 3H), 7.80 (dd, 1H), 7.90 (d, 1H), 8.00 (d, 1H), 8.10 (d, 1H), 8.86 (d, 1H), 9.08 (s, 1H) 11.00 (brd s, 1H) 11.82 (brd s, 1H); MS (APCI): 439.8

EXAMPLE 64:

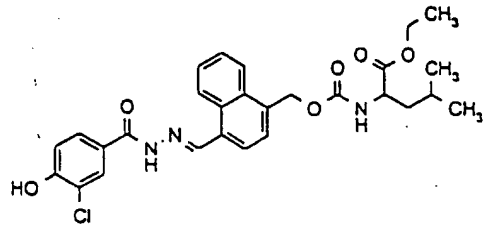
Cyclohexylcarbamic acid 4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-ylmethyl ester



^{1}H NMR (DMSO-d_6): δ 1.03 - 1.21 (m, 6H), 1.63 - 1.77 (m, 4H), 3.28 (m, 1H), 5.49 (s, 2H), 6.54 (d, 1H), 7.23 (d, 1H), 7.57 - 7.70 (m, 4H), 7.84 (d, 1H), 7.87 (d, 1H), 8.07 (m, 1H), 8.83 (d, 1H), 9.05 (s, 1H) 11.53 (s, 1H); MS (APCI): 479.9, 480.9.

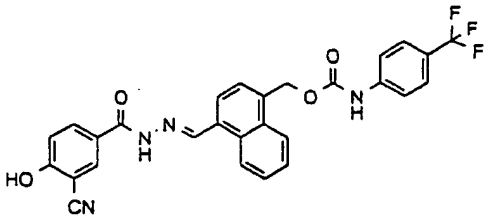
EXAMPLE 65:

2-{4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-ylmethoxycarbonylamino}-4-methylpentanoic acid ethyl ester

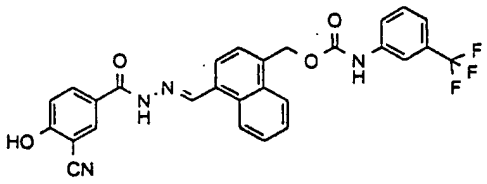


By use of the aforementioned methodology the following compounds of the formula (VII) may be produced:

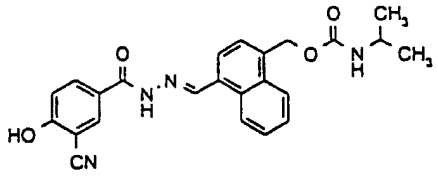
(4-Trifluoromethylphenyl)-carbamic acid 4-[(3-cyano-4-hydroxybenzoyl)-hydrazono-methyl]naphth-1-ylmethyl ester



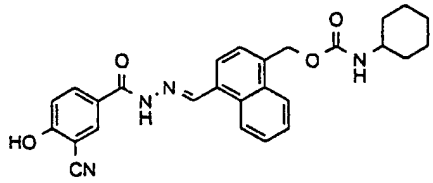
(3-Trifluoromethylphenyl)-carbamic acid 4-[(3-cyano-4-hydroxybenzoyl)hydrazono-methyl]naphth-1-ylmethyl ester



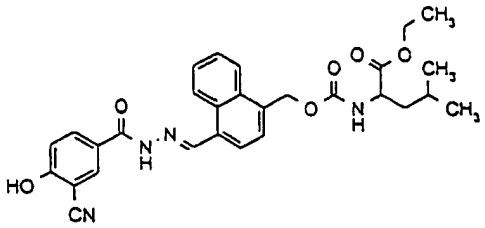
Isopropylcarbamic acid 4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-ylmethylester



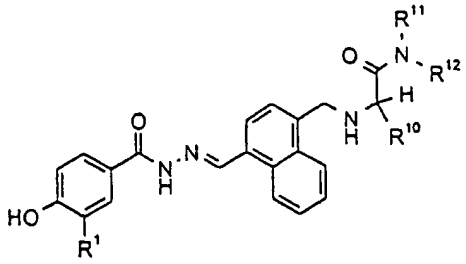
Cyclohexylcarbamic acid 4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-ylmethyl ester



2-{4-[(3-Cyano-4-hydroxybenzoyl)-hydrazonomethyl]naphth-1-ylmethoxy-carbonylamino}-4-methylpentanoic acid ethyl ester



In a further aspect the invention relates to the compounds of the general formula (VIII):



(VIII)

wherein

R^1 is chloro, fluoro, nitro or cyano;

R^{10} is hydrogen, C_{1-6}-alkyl or phenyl-C_{1-6}-alkyl;

R^{11} and R^{12} independently are hydrogen, C_{1-6}-alkyl, phenyl or phenyl-C_{1-6}-alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a preferred embodiment R^1 is chloro.

More preferred R^1 is cyano.

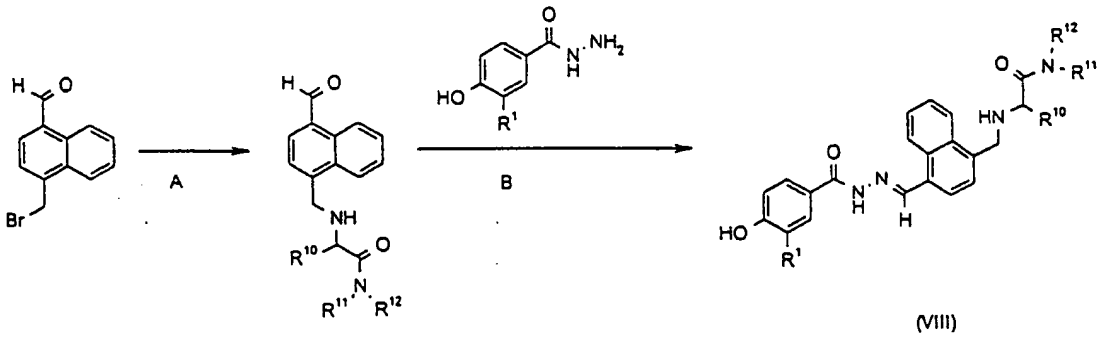
In another preferred embodiment R^{11} and R^{12} are both hydrogen.

In yet another preferred embodiment R^{10} is benzyl, *sec*-butyl or isobutyl, preferably benzyl.

The present invention is further illustrated by the following representative examples which are, however, not intended to limit the scope of the invention in any way.

General procedure for the preparation of compounds described by the formula (VIII):

SCHEME (VIII)



(VIII)

Step A: General procedure for the preparation of naphthylmethyl-amino-amides.

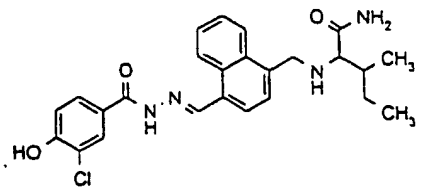
To a solution of bromomethylnaphthaldehyde in anhydrous dimethylformamide was added diisopropylethylamine (1.2 eq) and the desired amino-amide (1.1 eq). After stirring the reaction for four hours the mixture was diluted with ethyl acetate and washed with 1N HCl (2x), water (2x), brine, dried over $MgSO_4$, and concentrated. The products were purified via silica gel column chromatography.

Step B: General procedure for the preparation of hydrazones.

Hydrazones were prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation of the appropriate 3-substituted 4-hydroxybenzoic acid hydrazide and the above amino-amide-aldehydes.

EXAMPLE 66:

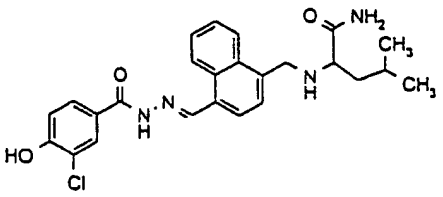
2-({4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-ylmethyl}amino)-3-methylpentanoic acid amide



^{1}H NMR (DMSO-d_6): δ 0.77 (t, 3H), 0.82 (d, 3H), 1.09 (m, 1H), 1.54 (m 2H), 2.86 (d, 1H), 3.95 (d, 1H), 4.20 (d, 1H), 7.09 (m 2H), 7.44 (brd s, 1H), 7.59-7.64 (m, 3H), 7.80 (d, 1H), 7.87 (d, 1H), 8.02 (s, 1H), 8.29 (d, 1H), 8.85 (d, 1H), 9.08 (s, 1H), 10.90 (brd s, 1H), 11.79 (s, 1H); MS (APCI): 466.9, 468.9.

EXAMPLE 67:

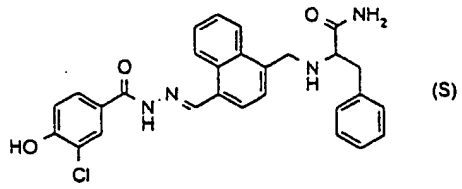
2-({4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-ylmethyl}amino)-4-methylpentanoic acid amide



^{1}H NMR (DMSO-d_6): δ 0.76 (d, 3H), 0.86 (d, 3H), 1.35 (d, 2H), 1.72 (oct, 1H), 3.09 (t, 1H), 3.17 (s, 1H), 3.36 (m, 3H), 4.00 (d, 1H), 4.20 (d, 1H), 7.08 (s, 1H), 7.10 (d, 1H), 7.47 (d, 1H), 7.59-7.67 (m, 3H), 7.80 (d, 1H), 7.87 (d, 2H), 8.01 (d, 1H), 8.26 (d, 1H), 8.84 (s, 1H), 9.08 (s, 1H), 11.80 (s, 1H); MS (APCI): 466.9, 468.9.

EXAMPLE 68:

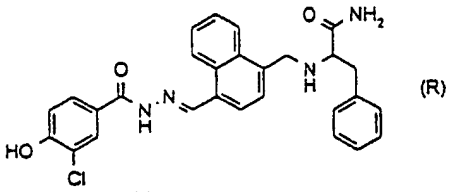
S-2-({4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-ylmethyl}amino)-4-methylpentanoic acid amide



^{1}H NMR (DMSO-d_6): δ 2.79 (m, 1H), 2.89 (m, 1H), 3.99 (d, 1H), 4.14 (d, 1H), 7.12 (m, 2H), 7.24 (m, 5H), 7.48 (m, 2H), 7.60 (m,1H), 7.64 (m, 1H), 7.80 (m, 2H), 8.01 (s, 1H), 8.11 (d, 1H), 8.82 (d, 1H), 9.06 (s, 1H), 11.00 (brd s, 1H), 11.79 (s, 1H); MS (APCI): 501.0, 502.0.

EXAMPLE 69:

R-2-({4-[(3-Chloro-4-hydroxybenzoyl)hydrazonomethyl]naphth-1-ylmethyl}amino)-3-phenylpropionamide

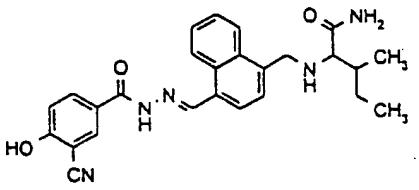


(R)

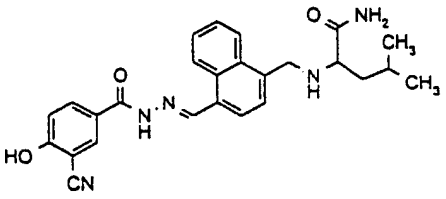
^{1}H NMR (DMSO-d_6): δ 2.74 (m, 1H), 2.88 (m, 1H), 3.98 (d, 1H), 4.16 (d, 1H), 7.11 (s, 1H), 7.20 (m, 1H), 7.24 (m, 5H), 7.47-7.60 (m, 3H), 7.64 (t, 1H), 7.79 (m, 2H), 8.01 (s, 1H), 8.11 (d, 1H), 8.80 (d, 1H), 9.06 (s, 1H), 11.78 (s, 1H); MS (APCI): 500.9, 502.9.

By use of the aforementioned methodology the following compounds of the formula (VIII) may be produced:

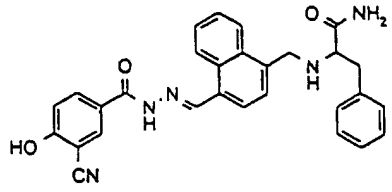
2-({4-[(3-Cyano-4-hydroxybenzoyl)-hydrazonomethyl]naphth-1-ylmethyl}amino)-3-methylpentanoic acid amide



2-({4-[(3-Cyano-4-hydroxybenzoyl)-hydrazonomethyl]naphth-1-ylmethyl}amino)-4-methylpentanoic acid amide

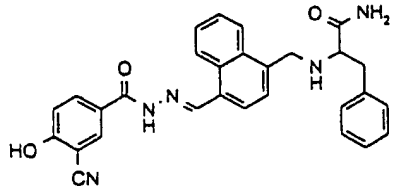


S-2-({4-[(3-Cyano-4-hydroxybenzoyl)-hydrazonomethyl] naphth-1-ylmethyl}amino)-4-methylpentanoic acid amide



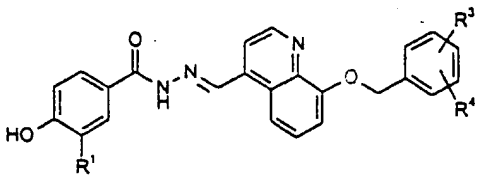
(S)

R-2-({4-[(3-Cyano-4-hydroxybenzoyl)-hydrazonomethyl]naphth-1-ylmethyl}amino)-3-phenylpropionamide



(R)

In a further aspect the invention relates to the compounds of the general formula (IX):



(IX)

wherein R^1 is chloro, fluoro, nitro or cyano; and

R^3 and R^4 independently are hydrogen, halogen, cyano, nitro, acetoxy, C_{1-6}-alkoxy, benzyloxy, trifluoromethyl, methylsulfonyl or C_{1-6}-alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a preferred embodiment R^1 is chloro.

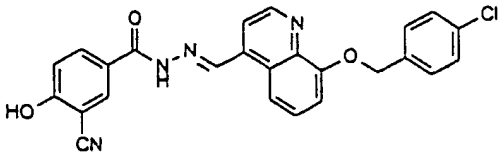
More preferred R^1 is cyano.

In a further preferred embodiment R^3 is hydrogen and R^4 is halogen.

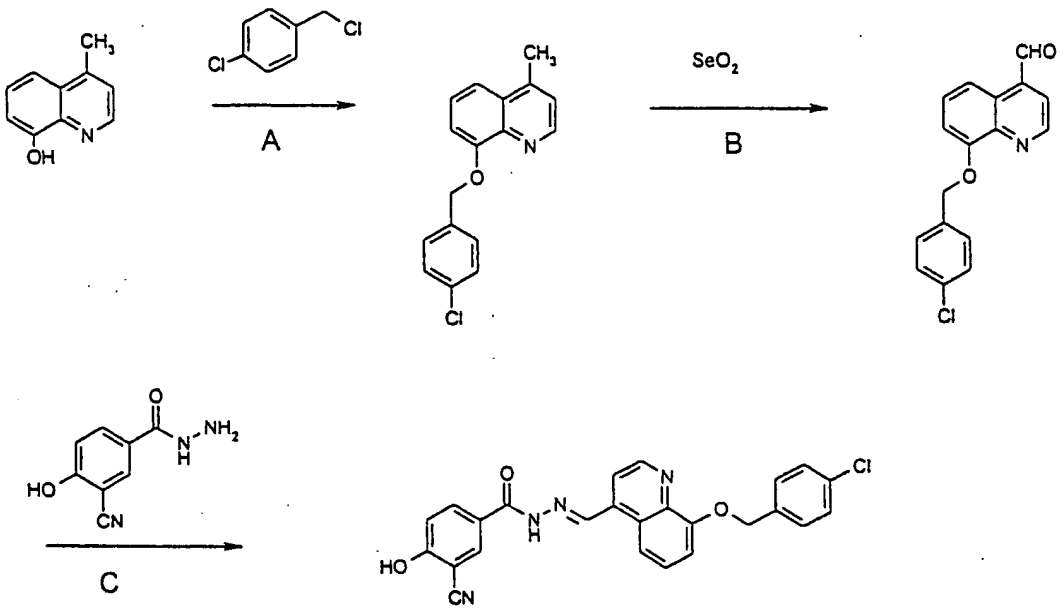
The present invention is further illustrated by the following representative examples which are, however, not intended to limit the scope of the invention in any way.

EXAMPLE 70:

3-cyano-4-hydroxybenzoic acid {[8-(4-chlorobenzyloxy])-4-quinolinyl]methylidene} hydrazide



SCHEME (IX)



Step A: 8-(4-Chlorobenzyloxy)-4-methylquinoline.

4-Methyl-8-hydroxy quinoline (2.65 g, 16.6 mmol) [prep. acc. P. Belser, S. Bernhard, U. Guerig, Tetrahedron 52, 1996, 2937 -2944] was dissolved in a warm solution of KOH (930 mg, 16.6 mmol) in ethanol (50 mL). The mixture was heated to reflux and a solution of 4-chlorobenzyl chloride (3.5 g, 21.7 mmol) in ethanol (20 mL) was added dropwise to the refluxing solution during a period of 30 min. Refluxing was continued for 16 hr. The solution was filtered by suction, and the filtrate was concentrated. The residue was diluted with ethyl acetate (100 mL), extracted with water (100 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (silicagel, hexane:ethyl acetate, 3:1) provided 1.6 g (34%) of a solid.

^{1}H NMR ($CDCl_3$): δ 2.69 (s, 3H), 5.41 (s, 2 H), 7.00 (d, J =7.7 Hz, 1H), 7.30 (d, J = 4.3 Hz, 1 H), 7.33 (d, J = 8.5 Hz, 2 H), 7.40 (dd, J = 7.7, 8.3 Hz, 1 H), 7.47 (d, J = 8.5 Hz, 2 H), 7.58 (d, J = 8.5 Hz, 1 H), 8.85 (d, J = 4.3 Hz, 1 H); GC-MS (pos.): 283.

Step B: 8-(4-Chlorobenzyloxy)-4-formylquinoline.

Selenium dioxide (620 mg, 5.6 mmol) was suspended in dioxane (5 mL); a few drops of water was added until a clear solution was obtained. The mixture was heated to 100°C and 8-(4-chlorobenzyloxy)-4-methyl quinoline (1.6g, 5.6 mmol) in dioxane (20 mL) was added

dropwise during a period of 2 hours. The mixture kept at 100°C for 4 hours, filtered hot and concentrated. The residue was treated with 1N HCl (200 mL), and filtered. The filtrate was neutralized with 3N NaOH, and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated. Recrystallization from toluene provided 1.02 g (62%) of a solid.

^{1}H NMR ($CDCl_3$): δ 5.42 (s, 2H), 7.12 (d, J =7.3 Hz, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.58 (dd, J = 8.1, 8.5 Hz, 1H), 7.85 (d, J = 4.3 Hz, 1H), 8.57 (d, J = 8.5 Hz, 1H), 9.25 (d, J = 4.3 Hz, 1H), 10.53 (s, 1H); GC-MS (pos.): 297.

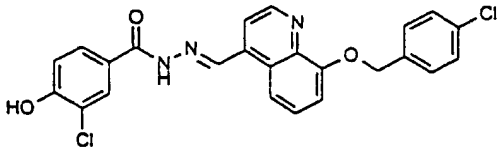
Step C: 3-Cyano-4-hydroxybenzoic acid {[8-(4-chlorobenzyloxy])-4-quinolinyl]methylidene} hydrazide.

The title compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation 8-(4-chlorobenzyloxy)-4-formylquinoline from step B and 3-cyano-4-hydroxy benzoic acid hydrazide.

^{1}H NMR (DMSO-d_6): δ 5.33 (s, 2H), 7.13 (d, J =8.8 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.63 (dd, J=J'=7.6 Hz, 1H), 7.86 (s, 1H), 8.08 (d, J=8.6 Hz, 1H), 8.21 (d, J=7.6 Hz, 1H), 8.26 (s, 1H), 8.95 (d, J=4.6 Hz, 1 H), 9.04 (s, 1H), 12.10 (s, 1H); IR (KBr): 2230, 1653, 1605 cm^{-1}; MS (APCI, pos.): 457.

EXAMPLE 71:

3-Chloro-4-hydroxybenzoic acid {[8-(4-chlorobenzyloxy])-4-quinolinyl]methylidene} hydrazide



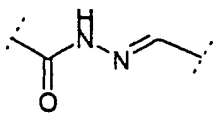
This compound was prepared according to the general procedure for the synthesis of alkylidene hydrazones from the condensation 8-(4-chlorobenzyloxy)-4-formylquinoline from step B and 3-chloro-4-hydroxy benzoic acid hydrazide.

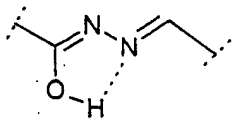
^{1}H NMR (DMSO-d_6): δ 5.33 (s, 2H), 7.06 (d, J =8.5 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.59 (m, 1H), 7.79 (dd, J = 1.9, 8.5 Hz, 1 H), 7.85 (d, J = 4.4 Hz, 1H), 8.00 (d, J=1.8 Hz, 1H), 8.20 (d, J=8.5 Hz, 1H), 8.26 (s, 1H), 8.94 (d, J = 4.4 Hz, 1H), 9.05 (s, 1H), 12.05 (s, 1H); MS (APCI, pos.): 466.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included in the scope of the invention.

Furthermore, one or more carbon-carbon or carbon-nitrogen double bonds may be present in the compounds which brings about geometric isomers. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included in the scope of the invention.

Furthermore, the compounds of the present invention may exist in different tautomeric forms, eg the following tautomeric forms:





It is intended that any tautomeric forms which the compounds are able to form are included in the scope of the present invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic,

benzenesulfonic, p-toluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compounds are able to form.

Furthermore, the pharmaceutically acceptable salts comprise basic amino acid salts such as eg lysine, arginine and ornithine.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of the present invention may form solvates with standard low molecular weight solvents using methods well known to the person skilled in the art. Such solvates are also contemplated as being within the scope of the present invention.

The invention also encompasses prodrugs of the present compounds which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of the present compounds which are readily convertible in vivo into the required compounds. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

The compounds according to the present invention act to antagonize the action of glucagon and are accordingly useful for the treatment and/or prevention of disorders and diseases in which such an antagonism is beneficial.

Accordingly, in a further aspect the invention relates to a compound according to the invention for use as a medicament.

The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound according to the invention together with one or more pharmaceutically acceptable carriers or excipients.

Furthermore, the invention relates to the use of a compound according to the invention for the preparation of a pharmaceutical composition for the treatment and/or prevention of a disorder or disease, wherein a glucagon antagonistic action is beneficial.

The invention also relates to a method for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial the method comprising administering to a subject in need thereof an effective amount of a compound according to the invention.

Owing to their efficacy in antagonizing the glucagon receptor the present compounds may be suitable for the treatment and/or prevention of any glucagon-mediated conditions and diseases.

Accordingly, the present compounds may be applicable for the treatment of hyperglycemia associated with diabetes of any cause or associated with other diseases and conditions, eg IGT (impaired glucose tolerance), insulin resistance syndromes, syndrome X, type I diabetes, type II diabetes, hyperlipidemia, dyslipidemia, hypertriglyceridemia, glucagonomas, acute pancreatitis, cardiovascular diseases, cardiac hypertrophy, gastrointestinal disorders, diabetes as a consequence of obesity etc. Furthermore, they may be applicable as diagnostic agents for identifying patients having a defect in the glucagon receptor, as a therapy to increase gastric acid secretions and to reverse intestinal hypomobility due to glucagon administration.

The present invention furthermore relates to methods of treating type I or type II diabetes or hyperglycemia which methods comprise administering to a subject in need thereof an effective amount of a compound according to the invention.

Moreover, the present invention relates to a method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to the invention.

The present invention is also concerned with the use of a compound according to the invention for the manufacture of a medicament for treating type I or type II diabetes or hyperglycemia, or for lowering blood glucose in a mammal.

In a further embodiment of the invention the present compounds are used for the manufacture of a medicament for the treatment and/or prevention of hyperglycemia.

In yet a further embodiment of the invention the present compounds are used for the manufacture of a medicament for lowering blood glucose in a mammal.

In another embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.

In still another embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.

In yet another embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

In yet another embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

In a further embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 1 diabetes. Such treatment and/or prevention is normally accompanied by insulin therapy.

In still a further embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of obesity.

In yet another embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of an appetite regulation or energy expenditure disorder.

Pharmaceutical formulations and administration methods

The compounds according to the invention, which may also be referred to as an active ingredient, may be administered for therapy by any suitable route including oral, rectal, nasal, pulmonal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal), the oral route being preferred. It will be appreciated that the preferred route will vary with the condition and age of the recipient, the nature of the condition to be treated, and the chosen active ingredient.

The compounds of the invention are effective over a wide dosage range. A typical dosage is in the range of from 0.05 to about 1000 mg, preferably of from about 0.1 to about 500 mg, such as of from about 0.5 mg to about 250 mg for administration one or more times per day such as 1 to 3 times per day. It should be understood that the exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated as well as other factors evident to those skilled in the art.

The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy,19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art.

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are on the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound according to the present invention contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the compound with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids, for example: maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylene salicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, pyruvic, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic, hydrochloric, hydrobromic, sulfuric, phosphoric or nitric acids. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses.

For parenteral administration, solutions of the novel compounds according to the present invention in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitable buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids,

fatty acids, fatty acid amines, polyoxyethylene or water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds according to the present invention and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	

Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

For nasal administration, the preparation may contain a compound according to the present invention dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

In a further aspect of the invention the present compounds may be administered in combination with one or more further pharmacologically active substances eg selected from antidiabetics, antiobesity agents, antihypertensive agents and agents for the treatment and/or prevention of complications resulting from or associated with diabetes.

Suitable antidiabetics comprise insulin, GLP-1 derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S which is incorporated herein by reference as well as orally active hypoglycaemic agents.

The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, insulin sensitizers, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents, compounds lowering food intake, PPAR and RXR agonists and agents acting on the ATP-dependent potassium channel of the β-cells.

In one embodiment of the invention the present compounds are administered in combination with insulin.

In a further embodiment the present compounds are administered in combination with a sulphonylurea eg tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg metformin.

In yet another embodiment the present compounds are administered in combination with a meglitinide eg repaglinide.

In still another embodiment the present compounds are administered in combination with a thiazolidinedione eg troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 to Dr. Reddy's Research Foundation, especially 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy]phenyl]-methyl]-2,4-thiazolidinedione.

In a further embodiment the present compounds are administered in combination with an α-glucosidase inhibitor eg miglitol or acarbose.

In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells eg tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

Furthermore, the compounds according to the invention may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART agonists, NPY antagonists, MC4 agonists, orexin antagonists, H3 antagonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3 agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK agonists, serotonin re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH agonists, uncoupling protein 2 or 3 modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR β agonists.

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy,19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

Experimental

In the following section binding assays as well as functional assays useful for evaluating the efficacy of the compounds of the invention are described.

Glucagon Binding Assay (I)

Binding of compounds to the glucagon receptor was determined in a competition binding assay using the cloned human glucagon receptor.

In the screening setup, antagonism was determined as the ability of the compounds to inhibit the amount of cAMP formed in the presence of 5 nM glucagon.

For full characterization, antagonism was determined in a functional assay, measured as the ability of the compounds to right-shift the glucagon dose-response curve. Using at least 3 different antagonist concentrations, the K_i was calculated from a Schild plot.

Receptor binding was assayed using cloned human receptor (Lok et al, Gene 140, 203-209 (1994)). The receptor inserted in the pLJ6' expression vector using EcoRI/SSt1 restriction sites (Lok et al) was expressed in a baby hamster kidney cell line (A3 BHK 570-25). Clones were selected in the presence of 0.5 mg/mL G-418 and were shown to be stable for more than 40 passages. The K_d was shown to be 0.1 nM.

Plasma membranes were prepared by growing cells to confluence, detaching them from the surface and resuspending the cells in cold buffer (10 mM tris/HCl), pH 7.4 containing 30 mM NaCl, 1 mM dithiothreitol, 5 mg/l leupeptin (Sigma), 5 mg/l pepstatin (Sigma), 100 mg/l bacitracin (Sigma) and 15 mg/l recombinant aprotinin (Novo Nordisk)), homogenization by two 10-s bursts using a Polytron PT 10-35 homogenizer (Kinematica), and centrifugation upon a layer of 41 w/v% sucrose at 95.000 * g for 75 min. The white band located between the two layers was diluted in buffer and centrifuged at 40.000 * g for 45 min. The precipitate containing the plasma membranes was suspended in buffer and stored at -80°C until required.

Glucagon was iodinated according to the chloramine T method (Hunter and Greenwood, Nature 194, 495 (1962)) and purified using anion exchange chromatography (Jørgensen et al,

Hormone and Metab. Res. 4, 223-224 (1972). The specific activity was 460 μCi/μg on day of iodination. Tracer was stored at -18°C in aliquots and were used immediately after thawing.

Binding assays were carried out in triplicate in filter microtiter plates (MADV N65, Millipore). The buffer used in this assay was 25 mM HEPES pH 7.4 containing 0.1% human serum albumin (Sigma, grade V). Glucagon was dissolved in 0.05 M HCl, added equal amounts(w/w) of HSA and freeze-dried. On the day of use, it was dissolved in water and diluted in buffer to the desired concentrations.

175 μL of sample (glucagon or test compounds) was added to each well. Tracer (50.000 cpm) was diluted in buffer and 15 μL was added to each well. 0.5 μg freshly thawed plasma membrane protein diluted in buffer was then added in 15 μL to each well. Plates were incubated at 25°C for 2 hours. Non specific binding was determined with 10^{-6} M glucagon. Bound and unbound tracer were then separated by vacuum filtration (Millipore vacuum manifold). The plates were washed once with 150 μL buffer/ well. The plates were air dried for a couple of hours, whereafter filters were separated from the plates using a Millipore Puncher. The filters were counted in a γ counter.

Functional Assay (I)

The functional assay was carried out in 96 well microtiter plates (tissue culture plates, Nunc). The resulting buffer concentrations in the assay were 50 mM tris/HCl, 1 mM EGTA, 1.5 mM $MgSO_4$, 1.7 mM ATP, 20 μM GTP, 2 mM IBMX, 0.02% tween-20 and 0.1% HSA. pH was 7.4 Glucagon and proposed antagonist were added in 35 μL diluted in 50 mM tris/HCl, 1 mM EGTA, 1.85 mM $MgSO_4$, 0.0222% tween-20 and 0.111 % HSA, pH 7.4. 20 μL of 50 mM tris/HCl, 1 mM EGTA, 1.5 mM $MgSO_4$, 11.8 mM ATP, 0.14 mM GTP, 14 mM iso-buthyl-methyl-xanthine (IBMX) and 0.1% HSA, pH 7.4 was added. GTP was dissolved immediately before the assay.

50 μL containing 5 μg plasma membrane protein was added in a tris/HCl, EGTA, $MgSO_4$, HSA buffer (the actual concentrations were dependent upon the concentration of protein in the stored plasma membranes).

The total assay volume was 140 µL. The assay was incubated for 2 hours at 37°C with continuous shaking. Reaction was terminated by addition of 25 µL 0.5 N HCl. cAMP was measured by the use of a scintillation proximity kit (Amersham).

Glucagon Binding Assay (II)

Receptor binding was assayed using the cloned human receptor (Lok et al, Gene 140, 203-209 (1994)). The receptor inserted in the pLJ6' expression vector using EcoRI/SSt1 restriction sites (Lok et al) was expressed in a baby hamster kidney cell line (A3 BHK 570-25). Clones were selected in the presence of 0.5 mg/mL G-418 and were shown to be stable for more than 40 passages. The Kd was shown to be 0.1 nM.

Plasma membranes were prepared by growing cells to confluence, detaching them from the surface and resuspending the cells in cold buffer (10 mM tris/HCl), pH 7.4 containing 30 mM NaCl, 1 mM dithiothreitol, 5 mg/l leupeptin Sigma), 5 mg/l pepstatin (Sigma), 100 mg/l bacitracin (Sigma) and 15 mg/l recombinant aprotinin (Novo Nordisk)), homogenization by two 10-s bursts using a Polytron PT 10-35 homogenizer (Kinematica), and centrifugation. The homogenate was resuspended and centrifuged again. The final precipitate containing the plasma membranes was suspended in buffer and stored at -80°C until required.

Binding assays were carried out in duplicate in polypropylene tubes or microtiter plates. The buffer used in this assay was 25 mM HEPES pH 7.4 containing 0.1% bovine serum albumin (Sigma, fraction V). Sample (glucagon (Bachem CA) or test compounds) was added to each tube or well. Tracer (~ 25000 cpm) was diluted in buffer and was added to each tube or well. 0.5 µg freshly thawed plasma membrane protein diluted in buffer was then added in aliquots to each tube or well. Tubes or plates were incubated at 37°C for 1 hour. Non specific binding was determined with 10^{-7} M glucagon. Bound and unbound tracer were then separated by vacuum filtration (Brandel). The tubes or wells were washed twice with buffer. The filters or plates were counted in a gamma counter.

Functional Assay (II)

The functional assay determined the ability of the compounds to antagonize glucagon-stimulated formation of cAMP in a whole-cell assay. The assay was carried out in borosilicate glass 12 x 75 tubes. The buffer concentrations in the assay were 10 mM HEPES, 1 mM EGTA, 1.4 mM $MgCl_2$, 0.1 mM IBMX, 30 mM NaCl, 4.7 mM KCl, 2.5 mM NaH_2PO_4, 3mM glucose and

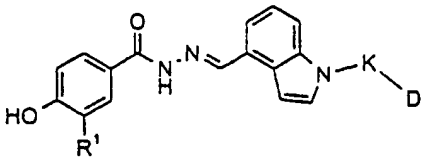
0.2% BSA. The pH was 7.4. Loose whole cells (0.5 mL, 10^6/ mL) were pretreated with various concentrations of compounds for 10 min at 37°C, then challenged with glucagon for 20 min. Some aliquots (500 µL) of cells were treated with test compounds (55 uL) alone to test for agonist activity. The reactions were terminated by centrifugation, followed by cell lysis with the addition of 500 µL 0.1% HCl. Cellular debris was pelleted and the supernatant containing cAMP evaporated to dryness. cAMP was measured by the use of an RIA kit (NEN, NEK-033). Some assays were carried out utilizing the adenylate cyclase FlashPlate system from NEN.

It should be apparent from the foregoing that other starting materials and other intermediate compounds can be substituted in the above procedures to prepare all of the compounds of the invention. The methods disclosed herein are based on established chemical techniques, as will be apparent to those skilled in the art, and therefore all of the compounds of the invention are broadly enabled by the preceding disclosure.

Accordingly, the invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive, and the scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All modifications which come within the meaning and range of the lawful equivalency of the claims are to be embraced within their scope.

Claims

1. A compound of the general formula (I):



(I)

wherein

R^1 is chloro, fluoro, nitro or cyano;

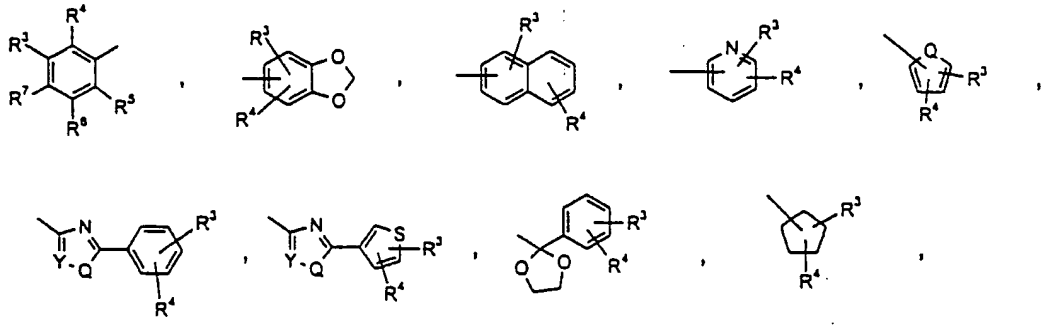
K is $-C(O)-(CH_2)_d-$, $-CH_2-CH_2-O-$ or $-CHR^2-$;

wherein

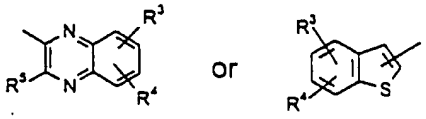
d is 0 or 1;

R^2 is hydrogen or C_{1-6}-alkyl ;

D is



or



wherein

Q is -O- or -S-;

Y is -CH= or -N=;

R^3, R^4, R^5, R^6 and R^7 independently are hydrogen, C_{1-6}-alkyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, halogen, carboxamido, hydroxymethyl, phenyl, dimethylamino, C_{1-6}-alkoxy or nitro;

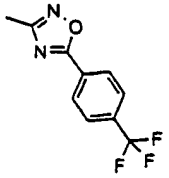
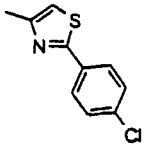
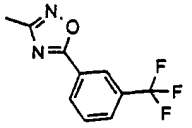
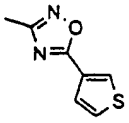
as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

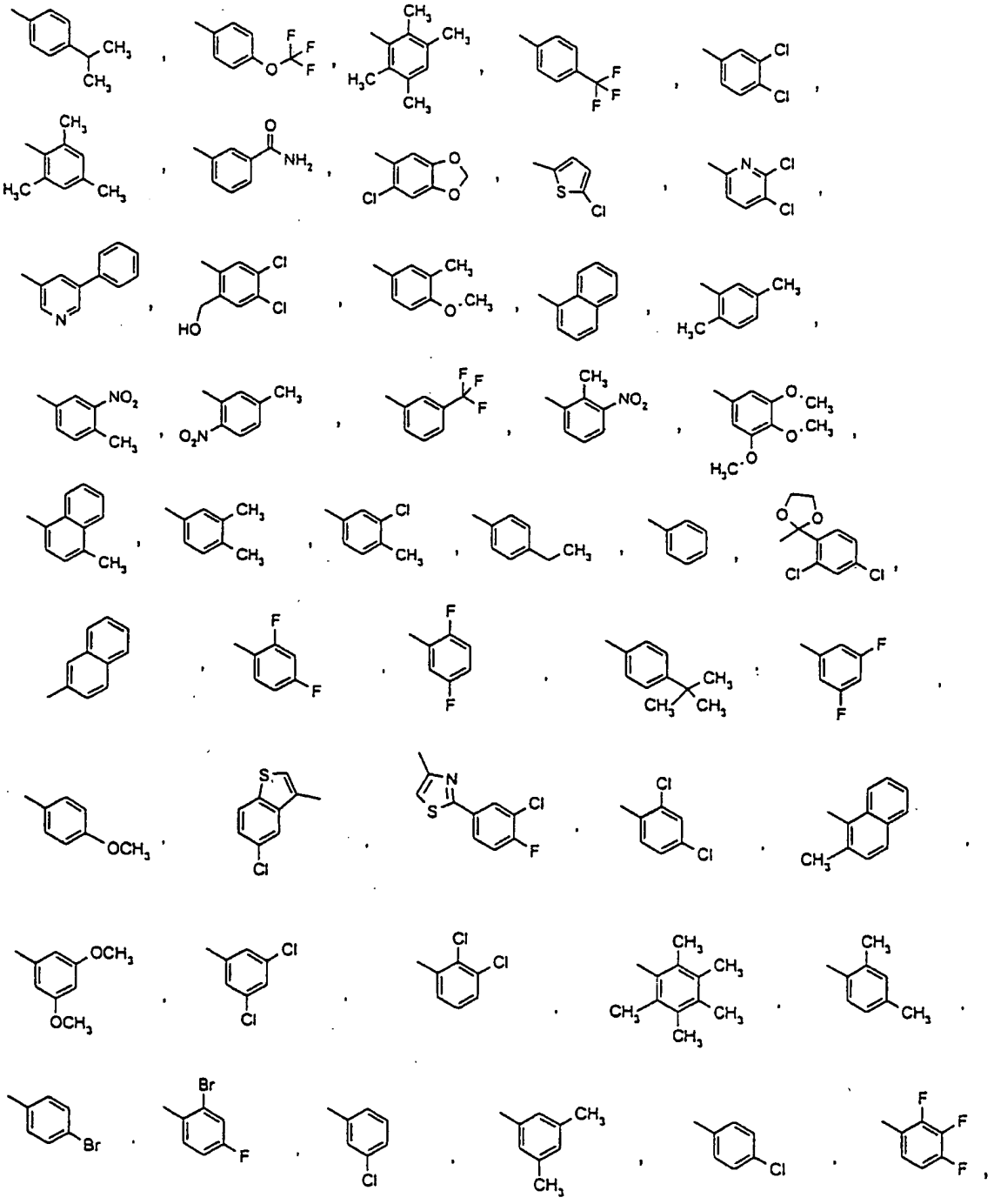
2. A compound according to claim 1, wherein R^1 is chloro or cyano, preferably cyano.

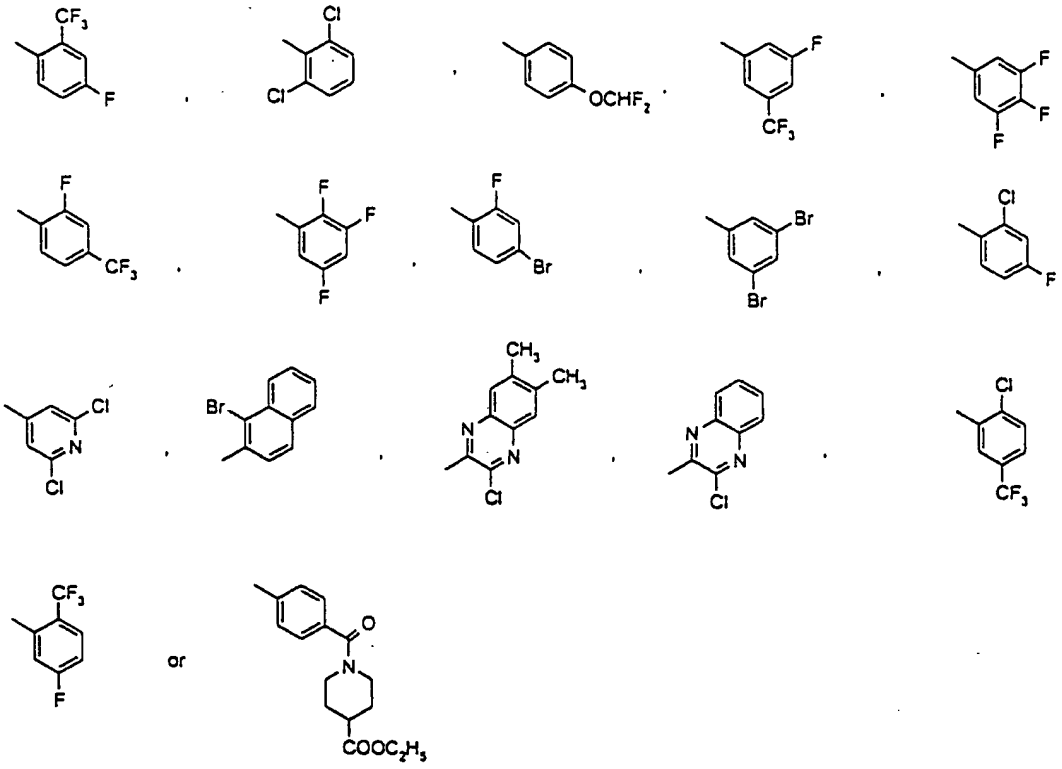
3. A compound according to claim 1 or 2, wherein K is $-CH_2-$ or $-CH(C_{1-6}\text{-alkyl})-$.

4. A compound according to claim 1 or 2, wherein K is -C(O)- or $-C(O)-CH_2-$.

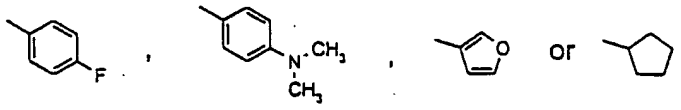
5. A compound according to any one of the claims 1 to 4, wherein
D is

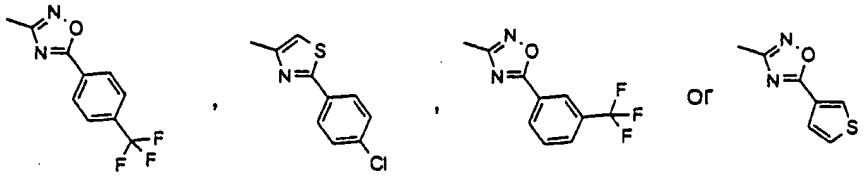




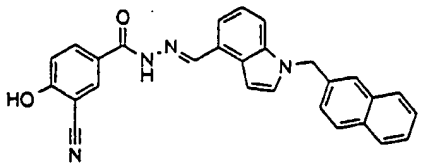
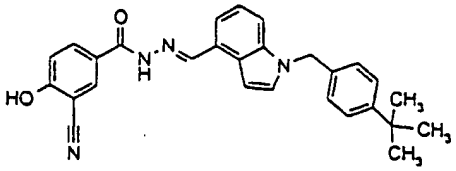
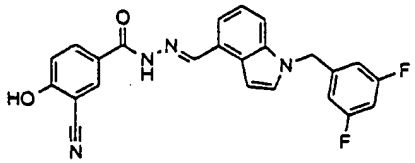
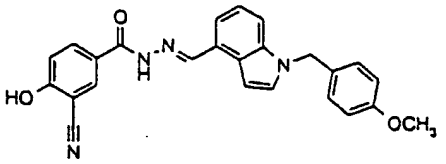
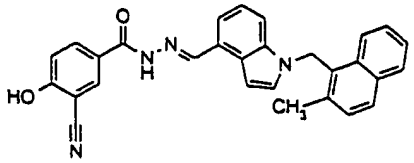
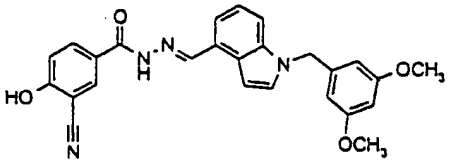
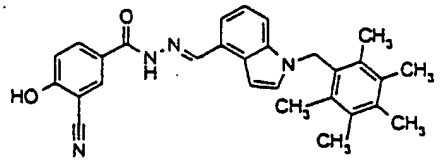
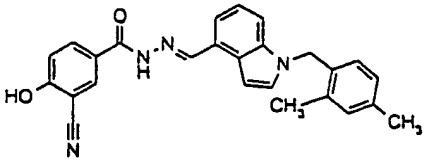
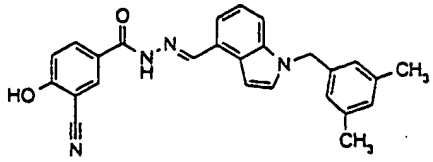
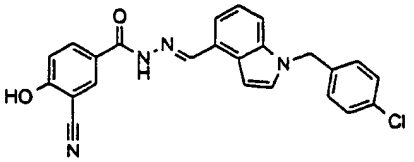
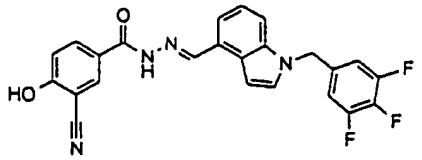
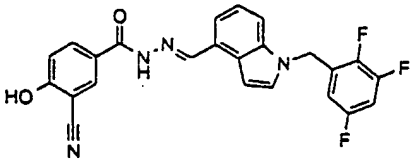
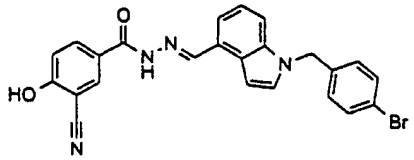
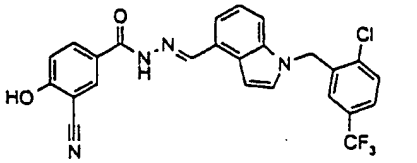
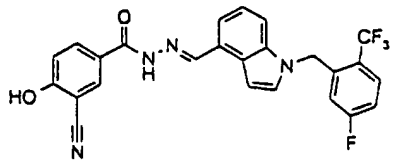
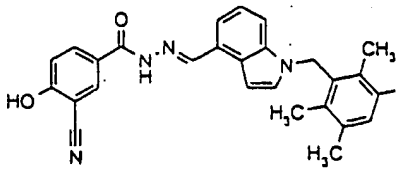
6. A compound according to claim 4, wherein D is



7. A compound according to claim 5, wherein D is



8. A compound according to claim 1, which is selected from

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 8 together with one or more pharmaceutically acceptable carriers or excipients.

10. A pharmaceutical composition according to claim 9 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 1 to 8.

11. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 8 or a composition according to claim 9 or 10.

12. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 8 or a composition according to claim 9 or 10.

13. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 1 to 8 or a composition according to claim 9 or 10.

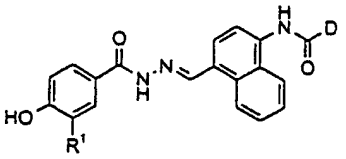
14. The method according to any one of the claims 11 to 13 comprising administering to a subject in need thereof an amount of the compound as defined in claims 1 to 8 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

15. Use of a compound according to any one of the claims 1 to 8 for the manufacture of a medicament for treating type I or type II diabetes.

16. Use of a compound according to any one of the claims 1 to 8 for the manufacture of a medicament for treating hyperglycemia.

17. Use of a compound according to any one of the claims 1 to 8 for the manufacture of a medicament for lowering blood glucose in a mammal.

18. A compound of the general formula (II):

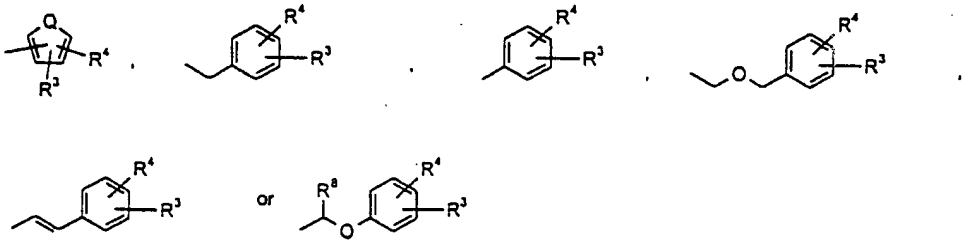


(II)

wherein

R^1 is chloro, fluoro, nitro or cyano; and

D is C_{1-6}-alkyl, C_{3-8}-cycloalkyl,



;

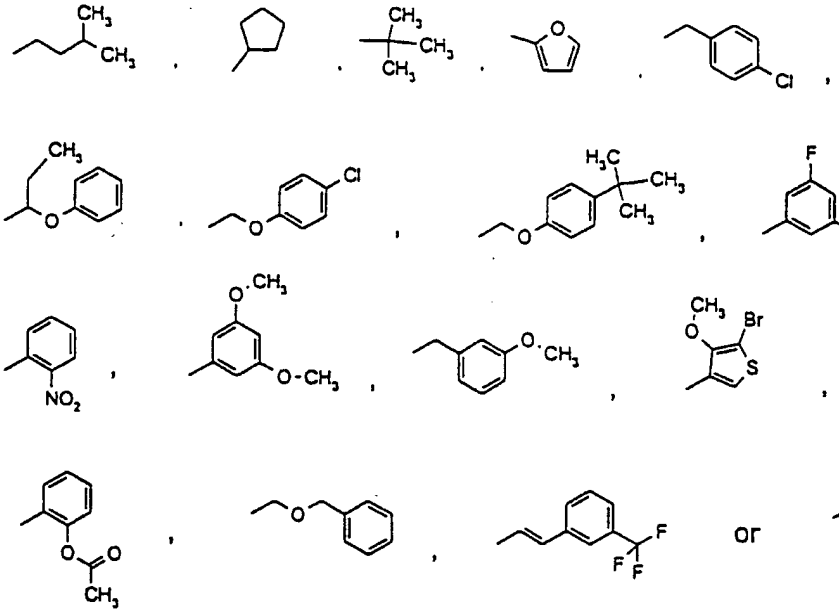
wherein R^3 and R^4 independently are hydrogen, halogen, cyano, nitro, acetoxy, C_{1-6}-alkoxy, benzyloxy, trifluoromethyl, methylsulfonyl or C_{1-6}-alkyl;

Q is -O- or -S-; and

R^8 is hydrogen or C_{1-6}-alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

19. A compound according to claim 18, wherein D is



20. A compound according to claim 18 or 19, wherein R^1 is chloro.

21. A compound according to claim 18 or 19, wherein R^1 is cyano.

22. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 18 to 21 together with one or more pharmaceutically acceptable carriers or excipients.

23. A pharmaceutical composition according to claim 22 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 18 to 21.

24. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 18 to 21 or a composition according to claim 22 or 23.

25. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 18 to 21 or a composition according to claim 22 or 23.

26. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 18 to 21 or a composition according to claim 22 or 23.

27. The method according to any one of the claims 24 to 26 comprising administering to a subject in need thereof an amount of the compound as defined in claim 18 to 21 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

28. Use of a compound according to any one of the claims 18 to 21 for the manufacture of a medicament for treating type I or type II diabetes.

29. Use of a compound according to any one of the claims 18 to 21 for the manufacture of a medicament for treating hyperglycemia.

30. Use of a compound according to any one of the claims 18 to 21 for the manufacture of a medicament for lowering blood glucose in a mammal.

31. A compound selected from the group consisting of:

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(2-trifluoromethylphenyl)acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

3-phenylpropynoic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}amide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-chlorophenyl)-acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3-chloro-phenyl)-acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-trifluoromethyl-phenylsulfanyl)acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

5-methoxybenzofuran-2-carboxylic acid {4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl)amide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

2-benzo[b]thiophen-3-yl-N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxy-phenyl}acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3,4-difluoro-phenyl)acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-chlorophenyl-sulfanyl)acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-3-(4-chlorophenyl)-propionamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof; and

N-{4-[(3-chloro-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-3-(4-cyanophenoxy)-acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

32. A compound selected from the group consisting of:

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(2-trifluoromethyl-phenyl)acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

3-phenylpropynoic acid {4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxy-phenyl}amide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-chlorophenyl)-acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3-chlorophenyl)-acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-trifluoromethyl-phenylsulfanyl)acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

5-methoxybenzofuran-2-carboxylic acid {4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl)amide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

2-benzo[b]thiophen-3-yl-N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxy-phenyl}acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3,4-difluorophenyl)acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(3-trifluoromethylphenyl)acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-3-(4-trifluoromethylphenyl)propionamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-2-(4-chlorophenylsulfanyl)acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-3-(4-chlorophenyl)propionamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof; and

N-{4-[(3-cyano-4-hydroxybenzoyl)hydrazonomethyl]-3-methoxyphenyl}-3-(4-cyanophenoxy)-acetamide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

33. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 31 or 32 together with one or more pharmaceutically acceptable carriers or excipients.

34. A pharmaceutical composition according to claim 33 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 31 or 32.

35. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 31 or 32 or a composition according to claim 33 or 34.

36. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 31 or 32 or a composition according to claim 33 or 34.

37. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 31 or 32 or a composition according to claim 33 or 34.

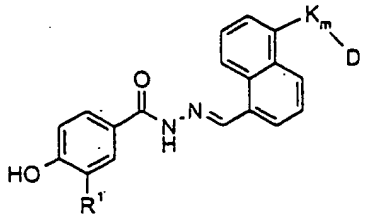
38. The method according to any one of the claims 35 to 37 comprising administering to a subject in need thereof an amount of the compound as defined in claim 31 or 32 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

39. Use of a compound according to any one of the claims 31 or 32 for the manufacture of a medicament for treating type I or type II diabetes.

40. Use of a compound according to any one of the claims 31 or 32 for the manufacture of a medicament for treating hyperglycemia.

41. Use of a compound according to any one of the claims 31 or 32 for the manufacture of a medicament for lowering blood glucose in a mammal.

42. A compound of the general formula (III):



(III)

wherein

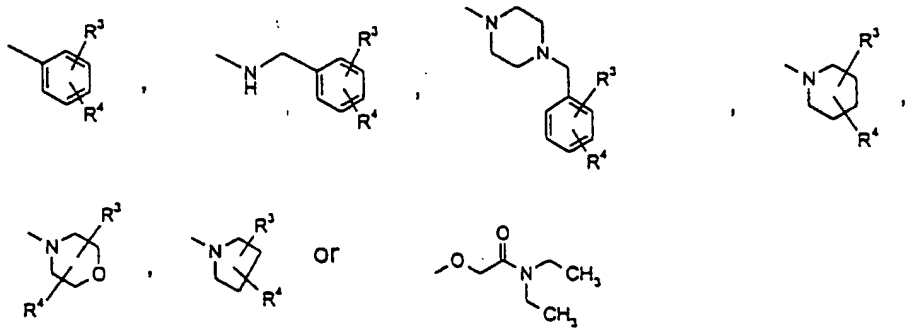
R^1 is chloro, fluoro, nitro or cyano;

K is

;

m is 0 or 1;

D is halogen, hydroxy,



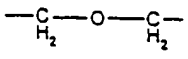
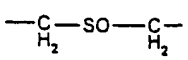
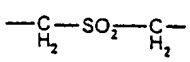
;

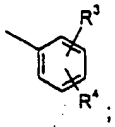
wherein

R^3 and R^4 independently are hydrogen, halogen, cyano, trifluoromethyl, trifluoromethoxy or C_{1-6}-alkyl;

with the proviso that

when K is

 ,  or  ;

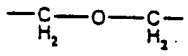
D is  ;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

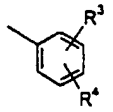
43. A compound according to claim 42, wherein R^1 is chloro.

44. A compound according to claim 42, wherein R^1 is cyano.

45. A compound according to any one of the claims 42 to 44, wherein m is 1, K is

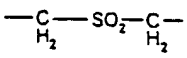


and D is

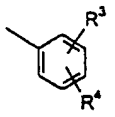


wherein R^3 and R^4 are as defined in claim 42.

46. A compound according to any one of the claims 42 to 44, wherein m is 1, K is

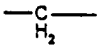


and D is

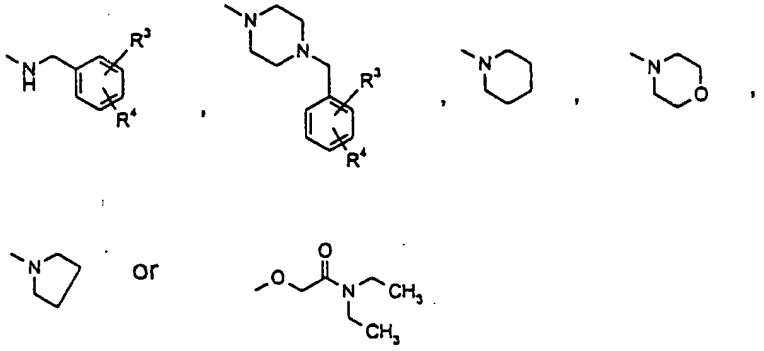


wherein R^3 and R^4 are as defined in claim 42.

47. A compound according to any one of the claims 42 to 44, wherein m is 1, K is



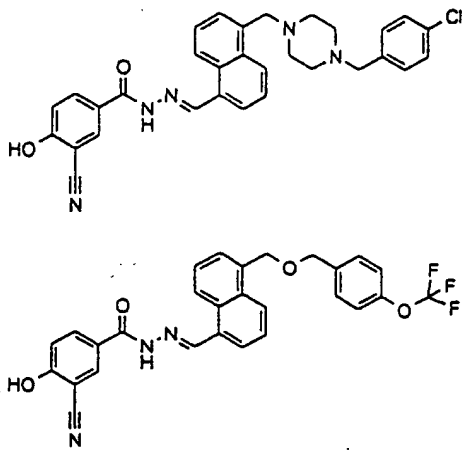
and D is halogen, hydroxy,

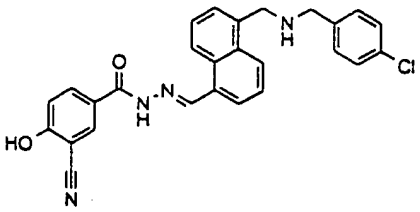


wherein R^3 and R^4 are as defined in claim 42.

48. A compound according to any one of the claims 46 to 48, wherein R^3 is hydrogen and R^4 is halogen, cyano, trifluoromethyl, trifluoromethoxy or C_{1-6}-alkyl.

49. A compound according to claim 42 which is selected from the group consisting of:





as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

50. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 42 to 49 together with one or more pharmaceutically acceptable carriers or excipients.

51. A pharmaceutical composition according to claim 50 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 42 to 49.

52. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 42 to 49 or a composition according to claim 50 or 51.

53. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 42 to 49 or a composition according to claim 50 or 51.

54. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 42 to 49 or a composition according to claim 50 or 51.

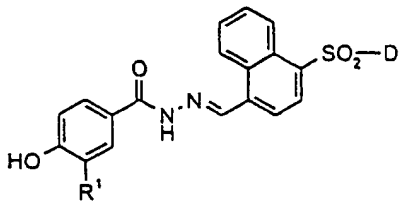
55. The method according to any one of the claims 52 to 54 comprising administering to a subject in need thereof an amount of the compound as defined in claim 42 to 49 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

56. Use of a compound according to any one of the claims 42 to 49 for the manufacture of a medicament for treating type I or type II diabetes.

57. Use of a compound according to any one of the claims 42 to 49 for the manufacture of a medicament for treating hyperglycemia.

58. Use of a compound according to any one of the claims 42 to 49 for the manufacture of a medicament for lowering blood glucose in a mammal.

59. A compound of the general formula (IV):

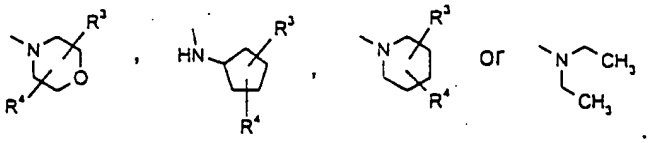


(IV)

wherein

R^1 is chloro, fluoro, nitro or cyano;

D is



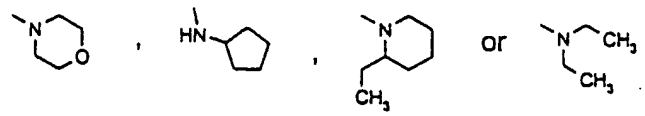
;

wherein

R^3 and R^4 independently are hydrogen, halogen, cyano, trifluoromethyl, trifluoromethoxy or C_{1-6}-alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

60. A compound according to claim 59, wherein D is



61. A compound according to claim 59 or 60, wherein R^1 is chloro.

62. A compound according to claim 59 or 60, wherein R^1 is cyano.

63. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 59 to 62 together with one or more pharmaceutically acceptable carriers or excipients.

64. A pharmaceutical composition according to claim 63 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 59 to 62.

65. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 59 to 62 or a composition according to claim 63 or 64.

66. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 59 to 62 or a composition according to claim 63 or 64.

67. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 59 to 62 or a composition according to claim 63 or 64.

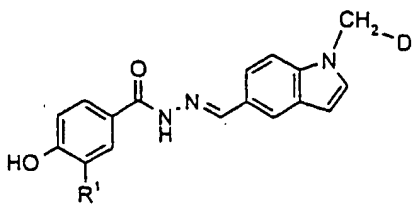
68. The method according to any one of the claims 65 to 67 comprising administering to a subject in need thereof an amount of the compound as defined in claim 59 to 62 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

69. Use of a compound according to any one of the claims 59 to 62 for the manufacture of a medicament for treating type I or type II diabetes.

70. Use of a compound according to any one of the claims 59 to 62 for the manufacture of a medicament for treating hyperglycemia.

71. Use of a compound according to any one of the claims 59 to 62 for the manufacture of a medicament for lowering blood glucose in a mammal.

72. A compound of the general formula (V):

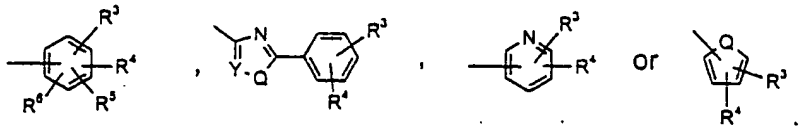


(V)

wherein

R^1 is chloro, fluoro, nitro or cyano;

D is



wherein

Q is -O- or -S-;

Y is -CH= or -N=;

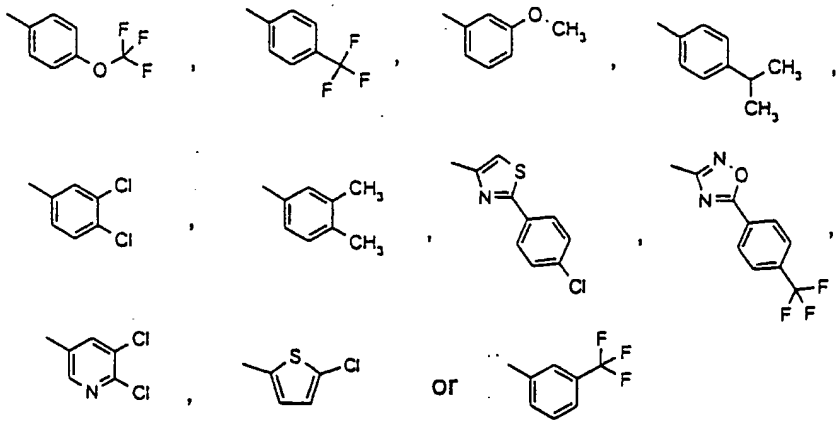
R^3, R^4, R^5 and R^6 independently are hydrogen, C_{1-6}-alkyl, trifluoromethyl, trifluoromethoxy, halogen or C_{1-6}-alkoxy;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

73. A compound according to claim 72, wherein R^1 is chloro.

74. A compound according to claim 72, wherein R^1 is cyano.

75. A compound according to any one of the claims 72 to 74, wherein D is



76. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 72 to 75 together with one or more pharmaceutically acceptable carriers or excipients.

77. A pharmaceutical composition according to claim 76 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 72 to 75.

78. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 72 to 75 or a composition according to claim 76 or 77.

79. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 72 to 75 or a composition according to claim 76 or 77.

80. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 72 to 75 or a composition according to claim 76 or 77.

81. The method according to any one of the claims 78 to 80 comprising administering to a subject in need thereof an amount of the compound as defined in claims 72 to 75 in the

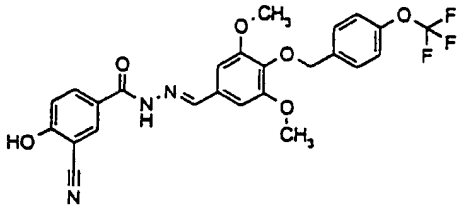
range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

82. Use of a compound according to any one of the claims 72 to 75 for the manufacture of a medicament for treating type I or type II diabetes.

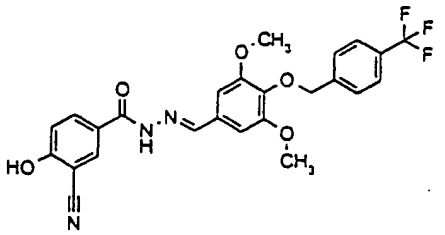
83. Use of a compound according to any one of the claims 72 to 75 for the manufacture of a medicament for treating hyperglycemia.

84. Use of a compound according to any one of the claims 72 to 75 for the manufacture of a medicament for lowering blood glucose in a mammal.

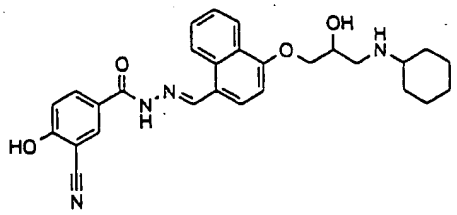
85. A compound selected from the group consisting of:



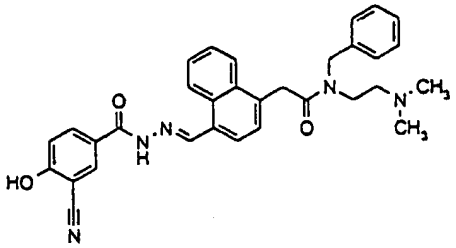
as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;



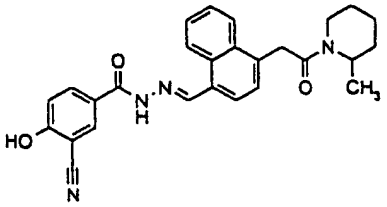
as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;



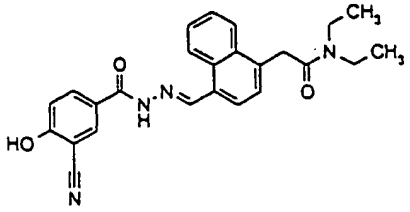
as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;



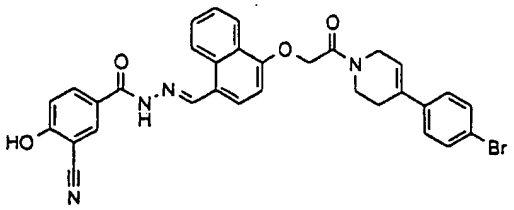
as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;



as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;



as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;



as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

86. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to claim 85 together with one or more pharmaceutically acceptable carriers or excipients.

87. A pharmaceutical composition according to claim 86 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to claim 85.

88. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to claim 85 or a composition according to claim 86 or 87.

89. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to claim 85 or a composition according to claim 86 or 87.

90. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to claim 85 or a composition according to claim 86 or 87.

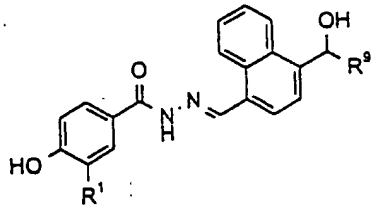
91. The method according to any one of the claims 88 to 90 comprising administering to a subject in need thereof an amount of the compound as defined in claim 85 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

92. Use of a compound according to claim 85 for the manufacture of a medicament for treating type I or type II diabetes.

93. Use of a compound according to claim 85 for the manufacture of a medicament for treating hyperglycemia.

94. Use of a compound according to claim 85 for the manufacture of a medicament for lowering blood glucose in a mammal.

95. A compound of the general formula (VI):



(VI)

wherein

R^1 is chloro, fluoro, nitro or cyano;

R^9 is C_{1-6}-alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

96. A compound according to claim 95, wherein R^1 is chloro.

97. A compound according to claim 95, wherein R^1 is cyano.

98. A compound according to claim 95 which is 3-cyano-4-hydroxybenzoic acid [4-(1-hydroxy-3-methylbutyl)-naphth-1-ylmethylene] hydrazide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

99. A compound according to claim 95 which is 3-cyano-4-hydroxy-benzoic acid [4-(1-hydroxy-2-methylpropyl)-naphth-1-ylmethylene] hydrazide as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

100. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 95 to 99 together with one or more pharmaceutically acceptable carriers or excipients.

101. A pharmaceutical composition according to claim 100 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 95 to 99.

102. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 95 to 99 or a composition according to claim 100 or 101.

103. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 95 to 99 or a composition according to claim 100 or 101.

104. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 95 to 99 or a composition according to claim 100 or 101.

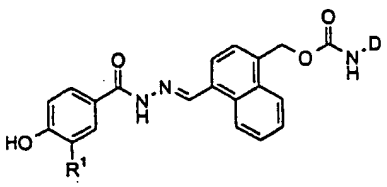
105. The method according to any one of the claims 102 to 104 comprising administering to a subject in need thereof an amount of the compound as defined in claims 95 to 99 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

106. Use of a compound according to any one of the claims 95 to 99 for the manufacture of a medicament for treating type I or type II diabetes.

107. Use of a compound according to any one of the claims 95 to 99 for the manufacture of a medicament for treating hyperglycemia.

108. Use of a compound according to any one of the claims 95 to 99 for the manufacture of a medicament for lowering blood glucose in a mammal.

109. A compound of the general formula (VII):

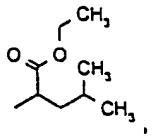


(VII)

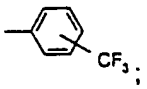
wherein

R^1 is nitro, fluoro, chloro or cyano;

D is C_{1-6}-alkyl,



or

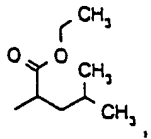


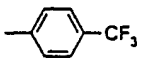
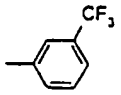
as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

110. A compound according to claim 109, wherein R^1 is chloro.

111. A compound according to claim 109, wherein R^1 is cyano.

112. A compound according to any one of the claims 109 to 111, wherein D is isopropyl,




or


113. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 109 to 112 together with one or more pharmaceutically acceptable carriers or excipients.

114. A pharmaceutical composition according to claim 113 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 109 to 112.

115. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 109 to 112 or a composition according to claim 113 or 114.

116. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 109 to 112 or a composition according to claim 113 or 114.

117. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 109 to 112 or a composition according to claim 113 or 114.

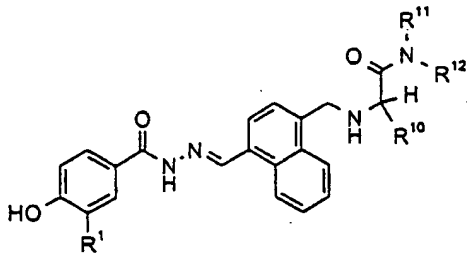
118. The method according to any one of the claims 115 to 117 comprising administering to a subject in need thereof an amount of the compound as defined in any one of the claims 109 to 112 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

119. Use of a compound according to any one of the claims 109 to 112 for the manufacture of a medicament for treating type I or type II diabetes.

120. Use of a compound according to any one of the claims 109 to 112 for the manufacture of a medicament for treating hyperglycemia.

121. Use of a compound according to any one of the claims 109 to 112 for the manufacture of a medicament for lowering blood glucose in a mammal.

122. A compound of the general formula (VIII):



(VIII)

wherein

R^1 is chloro, fluoro, nitro or cyano;

R^{10} is hydrogen, C_{1-6}-alkyl or phenyl-C_{1-6}-alkyl;

R^{11} and R^{12} independently are hydrogen, C_{1-6}-alkyl, phenyl or phenyl-C_{1-6}-alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

123. A compound according to claim 122, wherein R^1 is chloro.

124. A compound according to claim 122, wherein R^1 is cyano.

125. A compound according to any one of the claims 122 to 124, wherein R^{11} and R^{12} are both hydrogen.

126. A compound according to any one of the claims 122 to 125, wherein R^{10} is benzyl, *sec*-butyl or isobutyl.

127. A compound according to claim 126, wherein R^{10} is benzyl.

128. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 122 to 127 together with one or more pharmaceutically acceptable carriers or excipients.

129. A pharmaceutical composition according to claim 128 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 122 to 127.

130. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 122 to 127 or a composition according to claim 128 or 129.

131. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 122 to 127 or a composition according to claim 128 or 129.

132. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 122 to 127 or a composition according to claim 128 or 129.

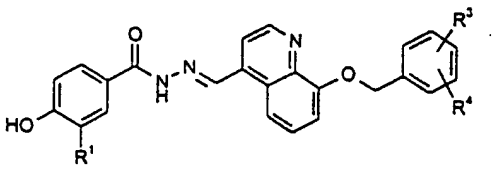
133. The method according to any one of the claims 130 to 132 comprising administering to a subject in need thereof an amount of the compound as defined in claims 122 to 127 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

134. Use of a compound according to any one of the claims 122 to 127 for the manufacture of a medicament for treating type I or type II diabetes.

135. Use of a compound according to any one of the claims 122 to 127 for the manufacture of a medicament for treating hyperglycemia.

136. Use of a compound according to any one of the claims 122 to 127 for the manufacture of a medicament for lowering blood glucose in a mammal.

137. A compound of the general formula (IX):



(IX)

wherein R^1 is chloro, fluoro, nitro or cyano; and

R^3 and R^4 independently are hydrogen, halogen, cyano, nitro, acetoxy, C_{1-6}-alkoxy, benzyloxy, trifluoromethyl, methylsulfonyl or C_{1-6}-alkyl;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

138. A compound according to claim 137, wherein R^1 is chloro.

139. A compound according to claim 137, wherein R^1 is cyano.

140. A compound according to any one of the claims 137 to 139, wherein R^3 is hydrogen, and R^4 is halogen.

141. A compound according to claim 137, which is

3-chloro-4-hydroxybenzoic acid {[8-(4-chlorobenzyloxy])-4-quinolinyl]methylidene} hydrazide or

3-cyano-4-hydroxybenzoic acid {[8-(4-chlorobenzyloxy])-4-quinolinyl]methylidene} hydrazide

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

142. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 137 to 141 together with one or more pharmaceutically acceptable carriers or excipients.

143. A pharmaceutical composition according to claim 142 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg of the compound according to any one of the claims 137 to 141.

144. A method of treating type I or type II diabetes, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 137 to 141 or a composition according to claim 142 or 143.

145. A method of treating hyperglycemia, comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 137 to 141 or a composition according to claim 142 or 143.

146. A method of lowering blood glucose in a mammal, comprising administering to said mammal an effective amount of a compound according to any one of the claims 137 to 141 or a composition according to claim 142 or 143.

147. The method according to any one of the claims 144 to 146 comprising administering to a subject in need thereof an amount of the compound as defined in claims 137 to 141 in the range of from about 0.05 mg to about 1000 mg, preferably of from about 0.1 mg to about 500 mg such as of from about 0.5 mg to about 250 mg one or more times per day such as 1 to 3 times per day.

148. Use of a compound according to any one of the claims 137 to 141 for the manufacture of a medicament for treating type I or type II diabetes.

149. Use of a compound according to any one of the claims 137 to 141 for the manufacture of a medicament for treating hyperglycemia.

150. Use of a compound according to any one of the claims 137 to 141 for the manufacture of a medicament for lowering blood glucose in a mammal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00705

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 209/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. Indian Chem. Soc., Volume 60, No 6, 1983, M. I. Husain et al, "Synthesis and Hypoglycemic Activity of Some New N-p-(Hydrozonocarbonyl)Phenyl-4-Substituted Benzene Sulphonamides" page 578 - page 579 --	1-10,15-17, 72-77,82-84
A,P	WO 9901423 A1 (NOVO NORDISK A/S), 14 January 1999 (14.01.99) --	1-10,15-17, 72-77,82-84
A,P	Patent Abstracts of Japan, abstract of JP 11-106371 A (Nisshin flour milling co ltd), 20 April 1999 (20.04.99) --	1-10,15-17, 72-77,82-84

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 April 2000	03.05.2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK99/00705

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-14, 78-81
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. ☒ Claims Nos.: 18-71, 85-150
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK99/00705

In view of the large number of claims which are both dependent and independent, the application in its entirety is so complex that an analysis of the claims not can be done by a reasonable effort. Therefore, the present application fails to comply with the requirements of Article 6 PCT to such an extent that a meaningful search on the basis of the claims is impossible. Consequently, the search has been carried out for claims 1-17 and 72-84 which concern compounds which contain an indol group.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/DK 99/00705

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9901423 A1	14/01/99	AU 7908398 A	25/01/99